THE CHILD WITH MONGOLISM

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(Congenital Acromicria)

With 85 Illustrations

By

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Dedicated to the parents whose devotion has contributed greatly to the human and scientific understanding of the child with mongolism

PREFACE

Although it is almost a hundred years since mongolism was first described by Langdon Down in 1866, scientific understanding of the condition has developed rather slowly. Mongolism exceeds all other morbid entities of severe mental retardation in number; and institutional admission rates of children with cerebral palsy, birth injuries and congenital malformations do not equal those of children with mongolism. A rate of three to four newborns with mongolism per thousand births has been reported from some hospitals, and an increase of patients has been observed in every country of the world. *This is the more alarming because a child with mongolism is usually* born into a normal family, with parents who often are far above average and siblings who exhibit outstanding mental capacities. Thus we deal *with a condition which takes a heavy toll of the offspring, who is* expected to be normal and yet fails to achieve an adequate mental and physical development.

The name "mongolism" is unfortunate and misleading because it has led many investigators astray into unfounded speculation and has detracted from intensive study of the pathology and etiology of this condition.

If we consider *the child with mongolism* rather than the variety of confusing symptoms, we begin to understand that the infant born with mongolism is a child whose prenatal development has not been completed in an adequate way A variety of physical aspects, more or less evident at birth, indicate some undetermined interference in the child's growth and differentiation. The result is that the child reveals certain symptoms *suggesting that his mental and physical development* may lag behind the average in later years Slight as these symptoms may be at the time of birth, the diagnosis implies that the child's *nervous system has not* reached the state of maturation which is expected in a full-term baby. The child with mongolism is therefore an infant whose physical and mental endowments and potentialities differ from those of the average child He shares with other members of his family many of the characteristics of both parents, and has inherent capability or disposition for further growth and development, but the constellation of symptoms indicates a certain impairment of his potentialities. While the child with cerebral palsy is impaired in

motor activity and often in some aspects of perception, the child with mongolism reveals a deceleration of physical and mental development, with the result that he grows and matures at a slower rate

Ever since mongolism was first described, all who came into contact with it—parents as well as scientists—have been baffled by the fact that one child in a perfectly normal family can differ so much from the other members. Modern research is thus clearly confronted with two problems:

1. To determine exactly why the child with mongolism grows and develops in a different way; and

2 To determine the underlying causes for such deviations in fetal growth

As to the first problem, the author has collected over a thousand clinical observations which were further enhanced by a careful study of 78 postmortem examinations, ranging from newborns to patients as old as 65 years This material has been systematically assembled over a period of almost 25 years. Some of the findings were first published in 1946 in *Mongolism and Cretinism*, a second edition of which followed three years later, in 1949. As far as measurements and anatomic and pathologic findings are concerned, some of the earlier material is integrated into the present edition. The collected data have been almost doubled in the past 10 years, however, and only those observations which could be confirmed in the second 10 year study are included here These observations throw light on the abnormal dynamics underlying the abnormal growth and development of the child with mongolism The anatomic data explain the structural deviations which account for the difference in appearance The organ pathology, including the anomalies in the endocrine glands—thyroid, adrenals, gonads and pituitary—provides evidence of underlying factors which interfere with normal growth and functioning. The endocrine pathology has been the subject of much scientific controversy, because it has been difficult to confirm through functional tests the essential disorder of abnormal cell metabolism. And yet the structural pathology is beyond criticism, and the failure of tests to confirm the observations is not due to the absence of symptoms but to the inadequacy of tests to gauge the deviations Improved technics are beginning to provide a better understanding of the nature of the growth disorder.

The present edition provides an almost entirely new chapter on the central nervous system of patients with mongolism The descriptions are augmented by many illustrations which may facilitate a better un-

derstanding of the anomalies of the nervous system even for those physicians, relatives and friends of the child who are not familiar with neuropathology. On the other hand, the newly discovered observations throw light on the profoundly abnormal brain metabolism. It is hoped that a clearer concept of the pathology of the nervous system will enable psychologists, teachers and even parents to have a better understanding of the difficulties in behavior and learning which may be exhibited by the child with mongolism.

The evidence furnished in this book will also facilitate a comprehension of the therapeutic difficulties. Not only do we deal with a deep-seated metabolic disorder of a cellular (molecular) nature, which must be corrected by adequate therapy, but such therapy must also overcome an abnormal prenatal development which is irreversible in some points. And yet, a better understanding of the condition will enable medical scientists to develop more adequate means of therapy. The vicious circle in which the child with mongolism is caught inhibits his development if he is left entirely to his own resources. Therapy has to break this vicious circle at some point, and stimulation with various supportive treatments represents a first step in this direction.

As to the etiology of mongolism, the book adds a wealth of new data to the observations which have been collected by various investigators. All the data at hand indicate that the child with mongolism is the product of some interference with prenatal development. Of the propounded theories—heredity, spontaneous mutation, fertilization of abnormal ovum, environmental factors in the early fetal stages—the accumulated evidence indicates that hereditary factors as well as spontaneous mutation can be excluded. The many factors which can be observed in the prenatal history of the mongoloid child provide circumstantial evidence that the abnormal development depends on temporary factors present in the maternal organism.

The controversial question of whether these factors operate at the time of fertilization or in the early stages of fetal development seems to have been brought nearer to an answer by new observations reported from France and England and confirmed by successive investigators in recent months. Chromosomal histology of various organ systems of children with mongolism indicates that the number of chromosomes—believed to be 46 in normal persons—is altered to 47 in the child who reveals the symptoms of mongolism. These observations mean that a small chromosomal particle, part of the chromatin structure of the nucleus of the cell, is present in addition to the

normal number of chromosomes. Since the chromosomes are the representatives of the genetic organizers and enzyme systems, the "supernumerary" chromosome particle is thought to interfere with cell metabolism on a molecular level. Much research must still be conducted as to the significance of these observations. Still pending is the question of whether such supernumerary chromosome particles may occur occasionally in human beings without much clinical significance, as has been observed in animal experiments. Another matter to be confirmed is whether this extra chromatin matter has the character of a true chromosome or represents a dormant chromatin particle of the cell nucleus. If these observations are fully clarified, the fertilization of an abnormal ovum resulting in the development of a mongoloid child may be indicated.

Under these aspects, the pathogenetic maternal factors would interfere with normal oogenesis and not operate after fertilization has taken place. Further research may reveal whether it is possible to discover the circumstances under which such abnormal oogenesis takes place. It may be stressed that the discovery of a "gene mutation" in the form of an abnormal chromosome would not paralyze therapeutic endeavors but on the contrary facilitate more rational therapy to correct abnormal cell metabolism.

The present book attempts to encompass the wealth of scientific observations which have been collected by the author and many different investigators, and which are rarely accessible and surveyed in one single presentation. Each reader may be interested in one or several aspects of the problem and so is given an opportunity to orient himself and find supportive evidence in different sections of the book.

The pediatrician and practitioner who deal with only a limited number of patients and seldom have an opportunity to see the great variety of phenomena associated with mongolism may find the necessary data for diagnosis and an understanding of the needs of the child with this condition.

The obstetrician, who sees these children first, may be helped in recognizing the condition at the time of birth. An increased knowledge of the prenatal factors may enable him to counsel mothers if they seek advice with regard to further pregnancies.

Psychologists and teachers who deal with these children in the community and in institutions will learn to understand [illegible]

[illegible] their child, as well as the events

which led to the birth of such a child. Many parents will be comforted to know that the scientific evidence indicates beyond doubt that mongolism has no relationship to hereditary disorders, and that a mongoloid child can be born potentially in any family, in certain circumstances.

Like the child with cerebral palsy who is now generally accepted, the child with mongolism needs the consideration, love and understanding that should be accorded any afflicted individual.

ACKNOWLEDGMENTS

The present book is based on almost 25 years of research, carried out in the Research Department of the Wrentham State School and since 1947 in the Research Department of the Walter E. Fernald State School, Waltham, Massachusetts. Many observations were collected in the community in various sections of this country and in other parts of the world.

I am indebted to the former Superintendent of the Wrentham State School, Dr. C. Stanley Raymond, and to the Superintendent of the Walter E. Fernald State School, Dr. Malcolm J. Farrell, whose steadfast interest and support have greatly facilitated the investigation. The research has been aided by the Corporation of the Fernald School, to whose Trustees I am indebted for their support and confidence.

Since September 1, 1956, Grant B-933 for a study of "neuropathological lesions in mental deficiencies" has been received from the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, making it possible to carry out an intensive study of the central nervous system in mongolism. The results are presented in chapter VI. Through the support of the National Institute, it has been possible to illustrate the pathology of the nervous system with 17 plates comprising 60 individual photographs and to make these reproductions accessible to the scientific world and the public without making the price of the book prohibitive.

I wish to express my gratitude for the collaboration of my co-workers in the laboratory, whose reliability and devotion were essential in this research. I am especially indebted to my principal secretary, Mrs. Dorothy Gillis, for her untiring support, and to Miss Mildred Schaefer, who assisted in the completion and editing of the manuscript. I am also deeply indebted to Mrs. Bettina Hirsch, the senior laboratory technician, who through all the years has conducted and supervised the tissue pathology. The splendid photographs and drawings are by Miss Ellen Sinclair, the charts by Mr. Jack Crown. I am also grateful to Mrs. Katherine Bakucz, Mr. Orrin Bradbury, and many other co-workers who assisted in various phases of the work.

I wish to thank my publisher, Dr. Henry M. Stratton, for his un-

limited support and generosity in facilitating the reproduction of so many illustrations. Permission to use a number of illustrations and figures from *Mongolism and Cretinism*, edition 2 (Grune & Stratton, 1949) is gratefully acknowledged.

Some progress in research has been reported by me in the International Record of Medicine (*165*:75, 1952), Quarterly Review of Pediatrics (*8*:79, 1953), and Archives of Pediatrics (*73*:391, 1956), to whose editors I am indebted for permission to use the following illustrations: International Record of Medicine, figures 1 and 3, pages 79 and 83; Quarterly Review of Pediatrics, figure 3, page 92; Archives of Pediatrics, figures 1 and 2, pages 393 and 394.

For illustrations based on other publications, due credit is given in the text.

CHAPTER I

HISTORY, FREQUENCY, TERMINOLOGY

HISTORY

When Langdon Down published his classic paper on "Ethnic classification of idiots" in 1866, he described mongolism for the first time, characterizing the mongoloid as

> a representative of the great mongolian race When placed side by side it is dif- [illegible]
>
> are roundish and extended laterally The eyes are obliquely placed and the internal canthi more than normally distant from one another. The palpebral fissure is very narrow The forehead is wrinkled transversely from the constant assistance which the levatores palpebrarum derive from the occipito-frontalis muscle in the opening of the eyes The lips are large and thick with transverse fissures. The tongue is long, thick, and much roughened The nose is small. The skin has a slight dirty yellowish tinge and is deficient in elasticity, giving the appearance of being too large for the body

This describes well the appearance of many mongoloid children between about 5 and 15 years of age, but it does not apply to the mongoloid newborn. Many a mongoloid baby would escape proper recognition if the diagnosis were too strictly based on stigmata given above

In the same year, Edouard Séguin, in his famous book on *Idiocy and Its Treatment by Physiological Methods*, gave a precise description of mongolism, which he considered a subgroup of cretinism. He wrote

> The lowland cretinism of Belgium, Virginia,—with its discrete goiter, its gray and dirty straw-colored skin, bears the same relation to idiocy and imbecility as the more extensive alpine variety So does the FURFURACEOUS CRETINISM with its milk white rosy and peeling skin, with its shortcomings of all the integuments, which give an unfinished aspect to the truncated fingers and nose, with its cracked lips and tongue, with its red, ectopic conjunctiva, coming out to supply the curtailed skin at the margin of the lids.

In the above, Séguin describes in a few words the essentials of the mongoloid features and includes an observation which has escaped

attention for more than half a century. It is interesting that he explains the epicanthal fold of the mongoloid child as caused by a curtailment of "skin at the margin of the lid." Had this observation received greater recognition there would not have been general approval of the idea that the mongoloid is a kinsman of the Mongolian race, and many contributions dealing with the strange "retrogression" to that race would not have been written.

John Fraser and Arthur Mitchell deserve credit for giving the first scientific report on mongolism. It was presented at a meeting of the Medico-Psychological Association, held at the Royal College of Physicians, Edinburgh, December 14, 1875, and published in July, 1876, in the Journal of Mental Science. It is interesting to note that when Dr. Mitchell first called Fraser's attention to the case which he presented, he was not aware of any literature on the subject. Mitchell, then Commissioner of Lunacy, said that this condition was known by the name of "Kalmuc idiocy," which he described as "a form of idiocy rarely met with in asylums, but nevertheless not really uncommon." The term was rejected by Dr. Ireland, who discussed Fraser's paper, and by the chairman of the meeting. Fraser defended it "on account of the form of the eyes and the size of the head." His report dealt with a 40 year old woman of whose skull he had made a fine reproduction. His description is a masterpiece of clinical observation, and he covered every aspect of the condition thoroughly Mitchell presented notes on 62 cases arranged according to age groups, emphasizing the short life span and brachycephaly, which he considered "almost invariably found." He noticed no hereditary factor, and no kinship of the parents, but observed bad health during pregnancy in a great number of cases. "The mental state is as distinct, as peculiar, and as steady as the physical. If the patients were brought together, they would be found to resemble each other strikingly in personal appearance. But more than this, they would also be found to resemble each other in character, in capacity, in likings and dislikings, in habits, in defects, in aptitudes." Mitchell recognized that these patients were not cretins but that they had some aspects in common with the "cretinoid" idiot

In 1877, Ireland included the mongoloid as a special type in his book on *Idiocy and Imbecility*. Shuttleworth in 1866 pointed out that these patients are in fact unfinished children, and that their peculiar appearance is really that of a phase of fetal life. "I do not mean that they are necessarily prematurely born, but that some cause has depressed the maternal powers, and there has been a defect of formative force. It is remarkable that, in my experience, nearly one half of these children are the last born of a long family. . . ."

The knowledge of mongolism increased steadily through a number of Anglo-American publications which dealt with such characteristics as the mouth and jaws (Robert Jones), the eyes (Oliver, 1891), the hands (Telford Smith, 1896), and the heart (Thomson and Garrod, 1898). In America, Wilmarth carried out extensive work on the pathology of idiocy as early as 1885, 1886 and 1890, when he published a survey on the examination of 100 brains of feeble-minded children

It is worthy of note that although Bourneville's great pioneer work on mental deficiency was begun in 1881, he did not deal with mongolism until 1900; after that, his publications on the subject followed each other at yearly intervals. Kassowitz (Vienna) took up the subject in the same year and studied its relationship to infantile myxedema.

Much interest was centered on the differentiation of mongolism [illegible]

[illegible], von Eiselsberg, Reverdin and Theodor Kocher, cretinism would still [illegible]

C [illegible]

edg[illegible]

and [illegible]. Although there are numerous contributions, the reports usually deal with only a few cases or with a single aspect of the condition. Considerably more material has been collected pertaining to the relationship between mongolism and maternal age, but even on this subject the interpretation is still a matter of argument

Brousseau presented the available material for the first time in 1928 His monograph offered a thorough review of the literature and the many aspects of the condition but did not attempt to underline the medical problems

At almost the same time (in 1929) van der Scheer published a German monograph which summarized his studies in Holland. The book abounds in personal experience. Unfortunately, van der Scheer committed himself to an interpretation of the whole pathology, which he explained on the basis of a narrow amnion sac that prevents the fetus from full development The "amnion sac theory," now associated with van der Scheer, is little supported by facts, and obscures the merits of this publication, which rest on its abundance of clinical material.

The medical interest in mongolism gathered [illegible]

Horst Geyer [illegible]

of mongolism

dition since it was based on very limited material. M. Schachter's Spanish monograph, *El Mongolismo,* followed in 1943. In 1946 the present author published the first complete American monograph (second edition, 1949) from a biological-medical point of view, analyzing the clinical pathology, neuropathology and endocrinology of mongolism and cretinism and comparing the two conditions. A smaller monograph was published in England by M. Engler in 1951.

FREQUENCY

Studies on the frequency of mongolism fall into three groups: (1) the incidence of mongolism among newborns; (2) the incidence among other forms of mental deficiency; and (3) the number of mongoloids living within the total population.

1. In order to be reliable, figures on the frequency of mongolism among newborns should include those mongoloids who are stillborn and those who die soon after birth. Beidleman made a study at the Boston Lying-in Hospital and reported that in the 14 years between 1930 and 1944 an average of 3 4 mongoloids per 1000 births was found with surprising uniformity. These statistics were based on *birth records in which mongolism was given as the primary* cause of death. Unfortunately, only in very modern teaching hospitals is the diagnosis of mongolism made at birth, and even then probably in no more than 95 per cent of the cases. If the child dies at birth, the registered diagnosis is usually congenital heart disease, prematurity or *asphyxiation, and not the underlying condition of mongolism.* Not all studies report such a high figure as the Boston study, however. Allowing for the cases that are either not recognized or not registered as mongoloids, it seems safe to assume that there are 2 to 3 instances of mongolism among 1000 births in unselected material.

Whether the incidence of mongolism varies with different geographic areas is not yet clearly established It will be lower, naturally, in hospitals in which there is a rather young group of mothers giving birth. A recent study by H W Kalb compares different statistics, and comes to the conclusion that the frequency falls into a rather narrow range.

The frequency of 2 to 3 instances of mongolism per 1000 births includes mothers in all age groups. That mongolism has a direct relationship to the age of the mother has been well established. Figure 1 represents the frequency of mongolism according to maternal age. From this table it is obvious that the incidence of mongoloid births varies between 1.25 and 1 68 per 1000 births among mothers who

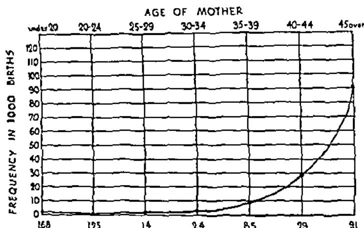


FIG 1 —Frequency of mongolism in relation to the age of the mother. In a maternal age group of 20 to 24, the frequency of mongolism is 1 25 per 1000 births The frequency rises slowly but steadily to the age group of 35 to 39, at which time 8 5 per 1000 mongoloid births are to be expected. At a maternal age of 40 to 44, the percentage rises to 29 per 1000, and at an age of 45 and over, as many as 91 per 1000 new born may be expected At a maternal age below 20, the incidence of mongolism is slightly higher than in the 20's, and newer data indicate that this difference may be of statistical significance.

are 18 to 29 years of age. After the age of 30 there is a definite rise [illegible] the [illegible] the [illegible] 29 infants per thousand are mongoloids, and at 45 years, the incidence will be 91 per thousand[1]

In figure 2 we have attempted to compile the actual number of mongoloids born in the United States, based on the national birth rate of 1956 The statistics would lead us to estimate that 11,700 mongoloids are born in one year. Local statistics seem to indicate that almost 400 mongoloids are born each year in New York City alone.

2 Studies of the incidence of mongolism among other forms of mental deficiency have several limitations. The significance of each study depends on many factors: what other forms of mental deficiency are used for comparison; whether the statistics are obtained from institutions for the mentally defective or from outpatient material; what age level is being considered. The age of the group selected for consideration is crucial, for the distribution of anomalies may be

dition since it was based on very limited material. M. Schachter's Spanish monograph, *El Mongolismo,* followed in 1943. In 1946 the present author published the first complete American monograph (second edition, 1949) from a biological-medical point of view, analyzing the clinical pathology, neuropathology and endocrinology of mongolism and cretinism and comparing the two conditions. A smaller monograph was published in England by M. Engler in 1951.

FREQUENCY

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The frequency of 2 to 3 instances of mongolism per 1000 births includes mothers in all age groups That mongolism has a direct relationship to the age of the mother has been well established Figure I represents the frequency of mongolism according to maternal age. From this table it is obvious that the incidence of mongoloid births varies between 1.25 and 1.68 per 1000 births among mothers who

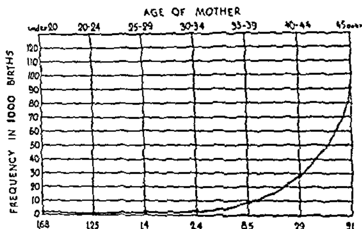


FIG. 1.—*Frequency of mongolism in relation to the age of the mother.* In a maternal age group of 20 to 24, the frequency of mongolism is 1.25 per 1000 births. The frequency rises slowly but steadily to the age group of 35 to 39, at which time 8.5 per 1000 mongoloid births are to be expected. At a maternal age of 40 to 44, the percentage rises to 29 per 1000, and at an age of 45 and over, as many as 91 per 1000 new born may be expected. At a maternal age below 20, the incidence of mongolism is slightly higher than in the 20's, and newer data indicate that this difference may be of statistical significance.

are 18 to 29 years of age. After the age of 30 there is a definite rise in the curve; and in the maternal age group between 35 and 39, the incidence has already risen to 8.5 mongoloid births per 1000. In the maternal age group of 40 years and older, 29 infants per thousand are mongoloids; and at 45 years, the incidence will be 91 per thousand!

In figure 2 we have attempted to compile the actual number of mongoloids born in the United States, based on the national birth rate of 1956. The statistics would lead us to estimate that 11,700 mongoloids are born in one year. Local statistics seem to indicate that almost 400 mongoloids are born each year in New York City alone.

2. Studies of the incidence of mongolism among other forms of mental deficiency have several limitations. The significance of each study depends on many factors: what other forms of mental deficiency are used for comparison; whether the statistics are obtained from institutions for the mentally defective or from outpatient material; what age level is being considered. The age of the group selected for consideration is crucial, for the distribution of anomalies may be

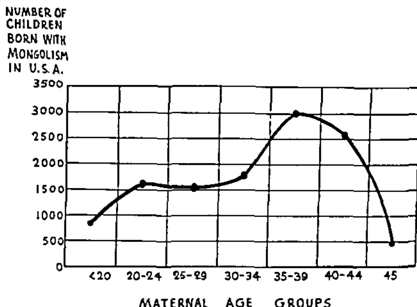


FIG. 2—Estimated number of children born with mongolism in the United States according to the different maternal age groups. It appears that about 12,000 newborn are afflicted each year in the United States

significantly altered over a few years by the life expectancy curve of each anomaly. In addition, some cases not associated with striking physical anomalies are not recognized in infancy and escape diagnosis for some years.

One picture of mongolism as it occurs among all forms of mental deficiency might be presented according to statistics from New York State, where all state school admissions are registered according to diagnosis.* Between April, 1947, and March, 1955, there were 12,066 admissions to state schools The combined familial and undifferentiated cases accounted for 62.9 per cent, mongolism, 9 8 per cent; post-traumatic, 6.6 per cent, postinfectious, 3 4 per cent, and miscellaneous, 6.2 per cent.

3. No authoritative count of the number of mongoloid persons currently living in the United States is available Even an estimate is difficult, as accurate birth statistics are not obtainable and the mongoloid's life expectancy has not been reliably calculated Twenty years ago, a Canadian publication stated that only one in four mongoloid infants saw his first birthday. The mortality rate of mongoloid children has decreased, however, to such an extent that a life expectancy of 30 years is a conservative estimate. At present, the oldest known mongoloid patient in an institution is over 74 years old

* Acta Genetica et Statistica Medica 5 301, 1955

That mongolism is generally increasing cannot be stated definitely, but several statistics from European countries seem to point in that direction. It remains to be seen whether the greater number of reported cases is due to an actual increase or to more accurate reporting of the condition.

TERMINOLOGY

The time-honored name "mongolism" is so well established that it will be many decades before it will disappear from the nomenclature and be replaced by a truly scientific term. Nevertheless, an attempt should be made to achieve uniformity of terminology and to eliminate inaccurate and misleading expressions. The term "mongoloid" refers to the Mongol-"like" appearance of these patients. It cannot be denied that there is a superficial resemblance to members of the Mongolian race in a number of cases, especially at a certain age, but it is incorrect to designate these children as "Mongolians." Even less appropriate is the term "Mongol," for this refers to the limited group of

Early members

objected to "nick

golian" because he is no more a Kalmuc than any other human being."

The term "unfinished children," introduced by Shuttleworth, was improved upon by John Thomson, who changed it to "ill finished." R Bennett Bean described the mongoloid as a "hypomorph white type."

The need for a better scientific expression is urgent in view of the fact that mongolism has been recognized in Negroes and Indians and is not rare in Chinese and Japanese children. Chinese doctors point out that they can distinctly recognize the condition in their population, but the term "mongolism" is certainly inadequate in such cases.

From an anatomic point of view, mongolism represents a growth deficiency which is the opposite of acromegaly. A more appropriate term, "congenital acromicria," was first used in 1907 by Arthur Schuller, who thus emphasized the characteristic

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whose development was "in opposition to acromegaly." As early as 1924, A. Lauche showed by histologic studies that the disorder of osseous growth in mongolism represented an acromicria. The present author demonstrated in 1940, through anatomic studies of the skull and extremities, that the term "acromicria" would indeed most adequately point out the growth deficiency.

This independent agreement of a number of investigators in the fields of pediatrics, radiology and histology indicates that the name "congenital acromicria" is well chosen.

CHAPTER II

THE DIAGNOSIS OF MONGOLISM AT BIRTH

Mongolism is present at birth. Thus the anomalies which are encompassed in the term must have developed in the prenatal period. This fact has two important implications (1) We are not able to study the events leading to mongolism in their very first stages because they occur in a child who is still *in utero*, hidden from the outside Hence the manifestations with which we deal are relatively late effects of the noxious factors which have interfered with normal development and differentiation, and which have changed the structural relationships of the organism and its functional coordination. (2) The newborn afflicted with mongolism suffers from the effects of a situation which interfered with normal fetal growth for at least several months Accumulated circumstantial evidence, to be discussed in detail in later chapters, indicates that the child who has developed mongolism has been subjected to deleterious conditions roughly from the beginning of the fifth week on. This does not necessarily mean that the noxious factors leading to mongolism operate only from the fifth week on, because it usually takes some time for any marginal pathogenic agent to exercise its full influence Whether the critical period is caused by external factors or is due to genetic inadequacy will also be discussed in a later chapter.

In order to understand the condition called "mongolism," one has to answer the question, what is mongolism at birth? It may be stated at the beginning that the old-established "characteristics" of mongolism—the Mongolian expression, the slanting eyes, the epicanthus—are the least reliable symptoms A large percentage of normal newborns (particularly in those geographic areas with Mongolian racial admixtures) have epicanthal folds, especially if the nose bridge is flat The mongoloid expression is often absent, and the examiner who bases his diagnosis of mongolism on such symptoms will miss the majority of cases All of the later events can only be understood if we comprehend the initial inhibitions of development which manifest themselves in their early stages at the time of birth.

Figure 3 is a diagrammatic comparison of the prenatal development, from four and one-half weeks of gestation to a full-term birth, of a normal child and a child with mongolism. The lower column illustrates the characteristic deceleration (slowing down of normal development) of differentiation and growth which occurs in mongolism. The critical stage begins a few weeks after fertilization and results in suppression and delay of developmental processes which are essential to normal functioning.

The mongoloid newborn shows a great number of deviations from the norm, often not too conspicuous, which vary in extent and distribution. Frequently these deviations are overlooked, and even the obstetrician is unaware of the condition. Many pediatricians are un-

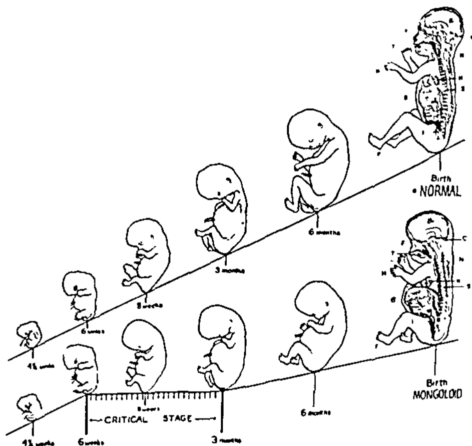


FIG 3.—Prenatal development from 4½ weeks to birth *Upper line* normal differentiation and growth. *Lower line:* deceleration of normal development leading to mongolism. The "critical stage" indicates the period in which the chromosomal, nuclear dysfunction seen in mongolism results in manifest dyschronism and deceleration of differentiation and development (heart, hands, eyes, brain, general growth)

able to establish the diagnosis with accuracy, often delaying a decision for three to six months—and yet the diagnosis of mongolism can be fully established at birth.

After inquiry at several lying-in hospitals, this investigator came to the conclusion that the most reliable symptom of mongolism at birth is the general hypotonia or flabbiness of the newborn, the lack of normal muscle tonus and stimuli responses which can be expected at that age The hypotonia, or "double-jointedness," of the newborn is a manifestation of cerebral immaturity. The normal tonus of the newborn indicates that the nervous system has reached a developmental stage which is "normal for term" As will be demonstrated in a later chapter, the central nervous system of the mongoloid newborn has not reached this stage and lacks motor and sensory readiness for extrauterine life. It may be emphasized at this point that the fundamental deficiency in mongolism is a condition of the nervous system. The presence of mental subnormality is essential for the diagnosis of mongolism, but all of the other characteristics associated with mongolism are incidentals which complete the picture of a fetal growth disorder.

If a hypotonic child, a suspected mongoloid, is examined carefully, a number of developmental anomalies may be noticed which involve all areas of the organism and several different organ systems One has to understand that mongolism is not a growth deficiency which involves one specific system alone; rather it appears to be the result of a fundamental disorder to which the fetus is subjected and which affects all metabolic processes.

Character ... The cal ... were stu ... anterior fontanel in a living child is a residue of the membranous skull, the ossification of which has failed to a large extent.

The condition of the skull sutures is of great diagnostic value. It is known that in mongolism the anterior fontanel is unusually large and closes after great delay. It has not yet been noted, however, that all sutures may be separated, and that in palpating the skull bones one may find that the sagittal suture is not in approximation and the parietal bones are separated ½ cm or more. The frontal suture, normally not present at birth, may be palpated down to the nasion even several months after birth. The same delay is recognizable about the posterior fontanel and the sutures which cross the sides of the skull That this delay or absence of union of ...

our child ...

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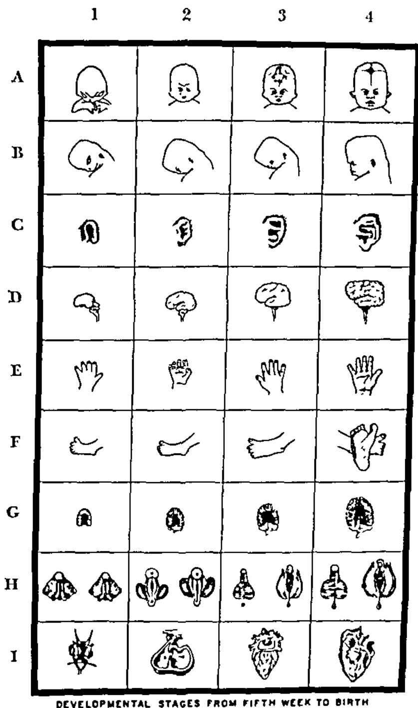


FIG. 4—Nine areas of developmental retardation most conspicuous in mongolism (From Benda. Mongolism. A comprehensive review Arch Pediat 73 391, 1956.).

(Legend continued on facing page)



Fig 5-a



Fig 5-b

Fig 5.—Superior view of the calvaria of two mongoloid infants (From Benda: Mongolism A comprehensive review. Arch Pediat. 73:391, 1956) (*A*) (frontal bone down) shows the extremely large "anterior fontanel" Ossification of membranous skull incomplete, leaving a much larger area unossified. Membranous skull grows from the sutures, which act like the epiphysis of the long bone. In mongolism, normal growth is delayed and the sutures are usually gaping (*B*) (frontal bone up) shows skull of another mongoloid infant (age, 6 months)

Normal growth of the membranous skull bones proceeds in proliferative ossification The delay of closure of the fontanelles and the open sutures are due to insufficient growth activity at the margins of the flat bones.

Usually the nose bridge is depressed, and the nose and upper jaw are short. The palate shows anomalies which are extremely characteristic of mongolism, and yet these anomalies have received little attention The palate shows flatness inside the dental ridge, and a high elevation in the midline, forming what is called a "steeple"

Fig 4 (*Continued*).—*Column 1* Developmental stage of fetus at 5 weeks There is some circumstantial evidence that the organogenetic period is fairly normal up to that time, and the developmental stage of the mongoloid does not differ essentially from that of other fetuses

Columns 2, 3, 4 Developmental stages at 3 months, at 6 months, and at term, respectively

Column 4 demonstrates nine aspects commonly abnormal in mongolism: (*A*) large anterior fontanel and open sutures, small slanting orbits, epicanthal folds, short nose, small mouth, (B) constricted facial features, underdeveloped nose, undeveloped ...

... ort thick neck; (C) fetal ... underdeveloped, imma- ... big toe and second toe; (*G*) abnormal palate, flat and broad inside dental ridge, high-arched midline; (*H*) incomplete sex differentiation—*left*, male small penis, often abnormal scrotum, *right*, female protruding clitoris, underdeveloped minor labia, large pouchy major labia; (*I*) patent foramen ovale, septum defect

palate. The remarkable aspect of this matter is that the palate cannot be described as flat or high, but as a combination of both. An explanation of this unusual feature can be found in embryonic studies, which show that the human palate is formed from two lateral processes which grow in a horizontal plane toward the midline, while the roof of the palate is formed from the lower surface of the nasion. In mongolism, the bones connected with the nasal cavity are underdeveloped and fail to reach the appointed level between the lateral processes of the palate. Hence, unable to form a moderately curved arch, the palate displays this combination of flatness and extreme elevation. In earlier studies this writer stated that cleft palate is relatively rare, but a number of cases with cleft palate has been observed since that time. A cleftlike formation of the palate is also seen, although the roof is not actually patent.

An analysis of the skull formation of the mongoloid infant demonstrated in anatomic and radiologic studies that the formation of the skull basis and facial bones constitutes the essential pathology of mongolism, regardless of the degree and variations in which it occurs. This anomaly is a growth deficiency in which certain areas of the facial skull are underdeveloped.

Nature as an architect follows two lines of development in completing the human skull. the formation of the "cerebral" skull, or the envelope of the central nervous system, and the formation of the "visceral" skull. The former provides support and protection for the central nervous system, and the latter a strong apparatus acting as a receiving and screening station, composed of the oral and nasal cavities and their supporting structures. The development of the cerebral skull during the second to fifth month of gestation consists primarily of the formation of the so-called *basilaris cranii*, a composite of numerous bones which serve the brain as a supportive floor and form the axis of the whole skull. Since the brain does not yet need the outer armor and has still to pass through the birth channel, which necessitates mobility of the protecting surface, the ossification of the membranous envelope lags far behind the stabilization of the cartilaginous foundation. However, since each animal (including man) needs, from the day of birth on, a strong oral system for providing the organism with food for its maintenance, Nature takes great pains in developing and stabilizing the masticatory-rhinal systems early so as to withstand the outside stress as soon as it arises Each line of development (of the cerebral and visceral skull) follows a rather independent course for a time, but the two systems are hinged upon the sphenoid body as the central supporting structure in which the visceral and cerebral skulls are joined together. The sphenoid

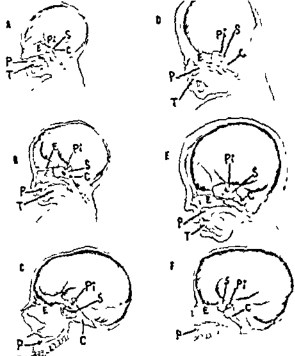


FIG 6—(From Benda, What is mongolism? (congenital acromicria) Internat. Rec Med 165 75, 1952)

A. Embryo* (47674) Calculated age, 16 weeks (C) clivus, (E) ethmoid, (P) hard palate; (Pi) pituitary, (S) sphenoid body, (T) tongue. Note clivus and sphenoid body with partial ossification, anterior sphenoid and ethmoid with crista cartilaginous, hard palate is firm and partially ossified, tongue within mouth behind maxillary ridge

B Embryo* (47706). Calculated age, 19 weeks Lettering same as in *A* Note progress in ossification and increase in size of sphenoid and ethmoid bones.

C. Diagram of normal adult skull. Lettering same as in *A*. Note development of sphenoid and frontal sinuses, great increase in development of visceral skull

D Mongoloid premature stillborn Lettering same as in *A* Note smallness of clivus and sphenoid body, shortness of anterior cavity, upright grading; shortness of visceral skull, short, thick hard palate; tongue too big, protrudes between jaws (For actual measurements, see text)

E Five months old mongoloid baby Lettering same as in *A* Note shortness of clivus, abnormal position of sphenoid, shortness of anterior skull cavity; shortness of hard palate, with tongue protruding.

F Mongoloid skull of patient about 20 years of age (compare with C) Lettering same as in *A* Note shortness of clivus, abnormal position of sphenoid, remnants of cartilage in sphenoid, shortness of anterior cavity, smallness of maxilla and shortness of hard palate The configuration of the skull is essentially the same as in the newborn, and the visceral skull has not participated in the extensive postnatal visceral development seen in the normal

* By courtesy of Dr Arthur T Hertig, Lying In Hospital, Boston, Mass.

palate. The remarkable aspect of this matter is that the palate cannot be described as flat or high, but as a combination of both. An explanation of this unusual feature can be found in embryonic studies, which show that the human palate is formed from two lateral processes which grow in a horizontal plane toward the midline, while *the roof of the palate is formed from the lower surface of the nasion.* In mongolism, the bones connected with the nasal cavity are underdeveloped and fail to reach the appointed level between the lateral processes of the palate. Hence, unable to form a moderately curved arch, the palate displays this combination of flatness and extreme elevation. In earlier studies this writer stated that cleft palate is relatively rare, but a number of cases with cleft palate has been observed since that time. A cleftlike formation of the palate is also *seen, although the roof is not actually patent.*

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in the abnormal shape of the mouth, in which the palatal processes are short and arched; this is a very typical feature. The underdevelopment is further evidenced internally by the laterally slanting, egg-shaped orbit holes, and externally by the slanting palpebral fissures

At birth the mongoloid skull does not yet have a definitely brachycephalic shape, but the fronto occipital diameter (normally 11.5 to 12 cm) appears somewhat shortened, though not in all cases. The width of the skull (biparietal diameter, normally 9.5 cm.) is normal or slightly subnormal. The circumference of the skull is, therefore, within normal range but below average (31 cm., or 13½ inches).

Diagnostically, the formation of the eyes is one of the most conspicuous anomalies. The mongoloid has short palpebral fissures which slant upward toward the lateral edge. At the medial corner the angle is covered by a skin fold, the "epicanthus" (*epi*, above, *canthus*, angle). However, it is interesting to note that this epicanthal fold is entirely different from the Mongolian epicanthus, which is due to the overlapping of the eyelid fold above the margin of the eyelid (fig 8). The eyelid of the mongoloid child is formed as in every European person, but has a sickle-shaped skin fold, plica marginalis fetalis, which runs around the medial angle of the eye and

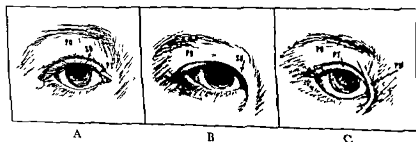


FIG 8 –Formation of external eye in (*A*) European races, (*B*) Mongolian races, and (*C*) mongoloid patients The superior palpebra is divided into the pars orbitalis (PO) and the pars tarsalis (PT), which are separated by the sulcus orbitopalpebralis superior (SO) In European races (A), the pars tarsalis (PT) is exposed In Mongolian races (B), the pars orbitalis (PO) overlaps the pars tarsalis with a skin fold, the pars tarsalis is therefore not visible The skin fold turns medially around the medial angle and partly covers the caruncula lacrimalis (epicanthus) In the mongoloid patient (C), the upper palpebra is formed as in (A), exposing the pars tarsalis of the upper lid The medial angle of the [illegible] is covered by a skin fold [illegible]

skin of the pars orbita [illegible]
the medial angle, also [illegible]
which normally disap[illegible]
mongoloids for many [illegible] [illegible] but persists in



Fig. 7.—(From Benda What is mongolism? (congenital acromicria) Internat Rec Med *165* 75, 1952) (*A, above*) X-ray, lateral view of mongoloid premature, stillborn Note extreme dorsoflexion of sphenoid, shortness of anterior cavity, retraction of nose bridge and smallness of maxilla (*B, below*) X ray of newborn mongoloid Note immaturity of skull with gaping sutures, retroflexion of sphenoid, shortness of anterior cavity and maxilla

body is composed of not less than 11 different ossification centers: through an elaborate schedule in the timetable of ossification and stabilization of the various joints, the normal skull achieves the alignment of the final specific human face. It is not surprising that any delay in this timetable, even a few days or weeks, may upset and disturb the whole inner relationship of visceral and cranial skull

Thus, an analysis of the skull anomalies found in newborn mongoloids indicates that the bone growth has undergone a temporary interruption, resulting in an underdevelopment and shortening of the facial bones. This underdevelopment is permanently manifested

in the abnormal shape of the mouth, in which the palatal processes are short and arched; this is a very typical feature. The underdevelopment is further evidenced internally by the laterally slanting, egg-shaped orbit holes, and externally by the slanting palpebral fissures

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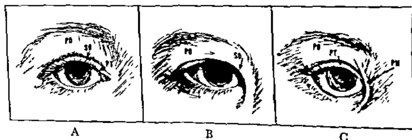


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ends beneath it in the skin of the sulcus infrapalpebralis. This fold has no relationship to features found in the Mongolian race. If the essential difference had been recognized from the very beginning, as Séguin did, the theory of racial retrogression could never have attained such general recognition. This plica marginalis of the mongoloid is a fetal feature, a residual, still present at birth, related to the underdevelopment of the nasion. This type of epicanthus is not rare in normal newborn babies, especially in races with rather flat nose bridges, as in the eastern European races. Therefore, it is *not surprising that in Russia, the Baltic states and eastern and central* Germany, between 30 and 40 per cent of the newborn babies have these folds. In normal children they usually disappear gradually. They also disappear in mongoloids, but at a much slower rate, and are rarely found beyond an age of 12 years. The majority of mongoloids have an epicanthus during the period between birth and 5 years of age. After the age of 10, the mongoloid eye has a more birdlike appearance. While the epicanthus is not a reliable sign, the peculiar smallness of the orbit holes is absolutely pathognomonic. As x-ray studies show, the orbit holes are egg-shaped and lack the size seen in normal children or cretins.

An examination of the whole organism reveals that a variety of developmental retardations can be observed, but most mongoloids *do not show stigmata in every possible area, and there is a great variety* of abnormal features. The ears are frequently involved and show abnormal fetal features. Hands, feet, neck, trunk and extremities in general are usually shorter than normal. The little finger is always short and occasionally curved, and the main hand lines often show patterns which are termed a "four finger line," meaning that only one rather straight line crosses the palm instead of the two curved lines of the normal hand. *However, it may be mentioned that the four finger line on both hands occurs as a genetic deviation in a certain percentage of the population and is, therefore, not a pathognomonic sign in itself.*

As further evidence of the fetal retardation present in the newborn, a congenital heart defect (usually consisting of an open foramen ovale or a larger septum defect) is present. Anomalies of sex development are frequent. In the female baby, in whom evaluation is rather difficult, Bleyer called attention, as early as 1937, to the underdevelopment of the minor labia, the rather large and often protruding clitoris, and *the pillow-like pouchy major labia.* More striking are the anomalies in the male mongoloid, in whom undescended testicles, usually at least one, are the rule. However, even more serious anoma-



Fig. 9—(*A, upper le*
line,' shortness of little
goloid child dorsal vie
morated thick skin (C ... Ear of a mongoloid child Note overlapping, straight upper helix and abnormal formation of *concha* with outstanding crus helicis crossing in the middle through *cavum conchae*. (*D, lower right*) Foot of a mongoloid child Note gap between first toe and second toe and skin crevice crossing the foot sole from the gap

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Fig 9—(*A, upper left*) Palm of a mongoloid child Note straight "four finger line," shortness of little finger and low-set thumb (*B, lower left*) Hand of a mongoloid child, dorsal view Note curvature and shortness of little finger, and marmorated thick skin (*C, upper right*) Ear of a mongoloid child Note overlapping, straight upper helix and abnormal formation of concha with outstanding crus helicis crossing in the middle through cavum conchae (*D, lower right*) Foot of a mongoloid child Note gap between first toe and second toe and skin crevice crossing the foot sole from the gap

TABLE 1.—*List of Symptoms Constituting the Diagnosis of Mongolism*
(According to Levinson, Friedman and Stamps)

Head	
A. Skull	
1 Open fontanel (beyond 1½ years)	16%
2. Open sutures	4%
3 Flat occiput	82%
B. Face	
1 Wrinkled forehead	14%
2 Red cheeks	66%
3 Rough and scaly cheeks	74%
C Eyes	
1 Slanting	88%
2 Epicanthus	50%
3 Blepharitis	38%
4 Strabismus	14%
5 Nystagmus	14%
6 Speckling of iris	30%
7 Double zone in iris	22%
D Ears	
1 Prominent	50%
2 Malformed	48%
3 Small or absent lobule	80%
E Nose	
1 Flat nose	44%
2 Small nose	54%
3 Flat nasal bridge	62%
F Mouth	
1 *Constantly open mouth*	62%
2 Small mouth	32%
3 Broad lips	36%
4 Irregular lips	28%
5 Dry lips	32%
6 Fissured lips	56%
7 Small teeth	56%
8 Conical lateral incisors	46%
9 Irregular alignment	68%
10 Widely spaced teeth	28%
11 Crowded teeth	38%
12 Large tongue	30%
13 Furrowed tongue	44%
14 Protruding tongue	32%
15. High-arched palate	74%
16 Narrow palate	52%
17 Cleft uvula	4%
18 *Raucous voice*	54%
19 Low-pitched voice	20%

TABLE 1—*Continued*

Trunk	
A Neck	
1 Broad	50%
2 Short	50%
B Chest	
1 Funnel chest	12%
2 Pigeon breast	14%
3 Flat nipples	56%
4 Heart murmur	28%
5 Dorsolumbar kyphosis	14%
C Abdomen	
1 Diastasis recti	76%
2 Umbilical hernia	4%
D Genitalia	
1 Small penis	50%*
2 Cryptorchism	20%*
3 Small scrotum	42%*
Extremities	
A General	
1 Acrocyanosis	28%
2 Marmoration	32%
3 Hyperextensible joints	88%
4 Hypotonic muscles	66%
B Hands	
1 Short and broad hands	74%
2 Flabby hands	84%
3 Palmar horizontal lines	48%
4 Short fingers	70%
5 Tapering fingers	52%
6 Short 5th finger	66%
7 Curved 5th finger	68%
8 Only 1 flexion furrow in 5th finger	10%
C Foot	
1 Gap between toes 1 and 2	44%
2 Toe 3 longer than toe 2	0%
3 Plantar furrow	28%

* Of males

lies are found in the form of an underdeveloped scrotum, short penis, hypospadia, and many other types of deviation

If we atte—

that

plete

...y. In practically every system,

external and internal, the organs have not reached a developmental stage comparable to the average. The evidence points to *decelerated* antenatal development.

The prenatal growth of mongoloids has been the subject of a study by Alwyn Smith and Thomas McKeown. They reported that the birth weight is lower and the period of gestation shorter than normal. Fifty-two and one-half per cent of mongoloids at birth weigh under 6 pounds, while among almost 5,000 single births in the same hospital, only 28.1 per cent weighed under 6 pounds Conversely, only 32 per cent of the mongoloids had a birth weight of 7 pounds or above, while in the control group 57.9 per cent of the newborn weighed over 7 pounds at birth. The largest single percentage (20 4 per cent) of mongoloids are born in the thirty-eighth week of gestation, while the peak of the 5,000 control cases (22.1 per cent) lies in the fortieth week. The lower weight of the mongoloid is not entirely due to the earlier onset of labor, and must be attributed in part to a slower rate of prenatal growth.

A study on the variability of mongolism by Abraham Levinson and co-workers also indicated lower birth weights in the mongoloid group These authors studied the frequency of a large number of symptoms given in table I

Unfortunately, when these statistics were compiled, a uniform age group was not used, and hence the configuration of anomalies in the mongoloid child is obscured For instance, the shortness of the skull is a most frequent symptom. In measuring over a thousand heads, I have found only two mongoloid children with skulls longer than 17 cm After reaching the age of two years, the overwhelming majority of mongoloid children have skulls ranging between 15 to 16 cm. in length, and only a few measure between 16 to 17 cm The majority of these children have brachycephalic skulls, the length of the skull being short in relation to the width, often the width equals the length and occasionally exceeds it However, brachycephaly does not depend on the length alone Some children with mongolism have very narrow heads so that the head appears long although the actual length is not normal Newborn children with mongolism usually have well formed heads in which the brachycephaly is not yet present The open mouth is a symptom which usually appears six to 12 months after birth and may then be present for several years. A discrepancy exists between the size of the tongue and the oral cavity. Many children with mongolism, especially those who have been treated, overcome this difficulty in later childhood The raucous voice depends on nutritional factors and the degree of thyroid deficiency, and can usually be avoided.

CHAPTER III

PHYSICAL DEVELOPMENT

Most of the anomalies of mongolism are not too conspicuous at the time of birth. Many physicians feel unable to establish a diagnosis before a child is three to six months of age or even later. The distinctive characteristics of this growth deficiency become more conspicuous as time goes on, because the child with mongolism does not develop like the average baby; the general pace of his progress is much slower than normal. He makes very little progress in the first year, whereas the normal infant undergoes an extremely rapid series of changes in physical appearance and mental performance. Thus the [illegible]

[illegible] ing degrees

Eyes

The eye symptoms in mongolism are varied and have attracted increasing interest in recent years, since they may provide some clues as *to the specific* [illegible] ith the *condition* [illegible] "mottled" (or m[illegible] ny ob[illegible]

[illegible] have hazel irises and a rather small percentage a more heavily pigmented *brown color.* This depends somewhat on the genetic background of the patient, but it is surprising that the mongoloid child *is often the only* member of a family to have blue eyes or a lesser degree *of pigmentation* than the others. The mottled or speckled iris—occasionally (without justification) called Brushfield spots—is sometimes seen in normal persons but rarely to the extent common in mongoloids. It is even present in [illegible]

[illegible] of the iris changes seems more

The stroma of the iris is especially thin in a high percentage of mongoloids, and shows certain patterns which are well demonstrated in figure 10. The abnormal stroma is conspicuous in the periphery, while the area immediately around the pupil often seems normal.

Of special interest are the so-called "lens opacities." Whether there is a true congenital cataract in mongolism is a matter of argument. Some investigators deny the presence of cataracts before the age of 6 years, while Skeller and Oster list six congenital cataracts among 32 patients with lens opacities but are not sure of the age at which the cataracts appeared. Igersheimer is of the opinion that the congenital cataract occasionally seen in mongolism is not of a specific nature. A study of the lens in mongoloid patients has produced evidence that a large percentage of patients gradually develop punctate or cerulean forms of lenticular changes which first appeared at about 6 years of age. The first manifestations are usually fine punctate opacities, which

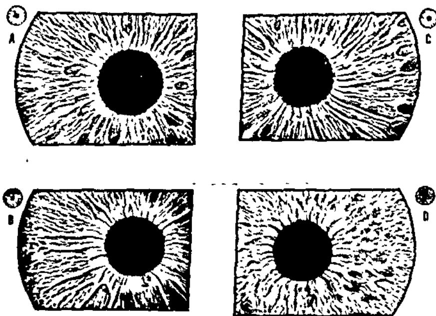


Fig. 10.—(Courtesy of Lowe, R. F. The eyes in mongolism. Brit. J. Ophthalmol., March, 1949.) (*A*) Iris of mongoloid, age 35 years. Blue iris showing white speckling, fine stroma, posterior pigment epithelium and sphincter. (*B*) Iris of mongoloid, age 47 years. Thin gray iris showing advanced stromal atrophy and thick strands becoming very thin towards the periphery. (*C*) Iris of mongoloid, age 37 years. Thin gray iris showing white speckling, and very pronounced atrophy of stroma at periphery (ciliary region). (*D*) Iris of mongoloid, age 32 years. Hazel iris, thickly pigmented around the pupil where the stroma is coarse, showing characteristic thinning of the stroma towards the periphery.



FIG 11 —Face of a mongoloid girl, 9 years of age Note thin straight hair, slanting almond shaped eyes, plica marginalis (epicanthus) especially of left eye, strabismus, flat nose bridge, fissured dry lips and tongue

increase in number and size and form flake-like dots. The onset seems to be in the cortex of the lens and not in the subcapsular region

Strabismus, convergent or occasionally divergent, is frequent in young children with mongolism (fig 11) This condition corrects itself in later years in about two-thirds of the cases, but remains throughout life and is predominantly convergent and horizontal in the other third

Nystagmus is also frequent in the earlier years but gradually disappears, remaining throughout life in less than 10 per cent of the patients Refractive errors are extremely common, in my experience, and are often conspicuous clinically—for instance, by the way that mongoloid children write and read the position of the head and its

distance from the working surface. However, about one-quarter of the children seem to have fairly average refraction. While myopia is seen frequently and was noted by Lowe in one-third of his patients, Skiller and Oster report a rather high incidence (67 per cent) of varying degrees of hypermetropia.

Interpupillary distances average between 52 and 60 mm. (Lowe), which is in line with Brushfield's observations. According to Lowe, the distance is shorter than in the normal adult population because the head of the mongoloid is generally smaller.

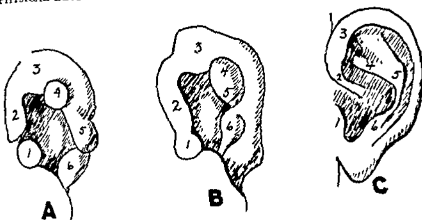
Several other anomalies are connected with the eye. The skin of the eyelids is abnormally thick, and the conjunctivae are susceptible to inflammation and chronic changes which lead to thickening and tumefaction The ciliary body of the lower lid is frequently enlarged The eyelashes are short and sparse Frequently there is chronic blepharitis, and ectropion is not rare.

Ears

Anomalies in formation of the external ear are frequent. This is not surprising in view of the fact that ear anomalies are often associated with all types of mental deficiency; abnormal ear formation seems a rather sensitive indicator of developmental anomalies. The type of pathology is not constant. The various shapes of the ear have not yet been properly classified, and the terminology is inadequate. An understanding of the anomalies in mongolism may be gained from a glance at figure 12 (diagram of ear development). In infancy and early childhood, the mongoloid ear is frequently very small and gives the impression of fetalism The upper helix overlaps more than usual, and the margin forms a right angle to the descending part of the ear. The tragus may be flattened, and borders the entrance to the ear in a straight line. Later in life, many mongoloids have extremely outstanding "lop" ears, with flat or absent helix. The site of the ear is frequently low.

Mouth and Tongue

The mucosa of the mouth and lips becomes abnormal early in life. The lips then appear fissured and dry. The tongue undergoes fissuration and hypertrophy of the papillae. The fissuration of the tongue is frequently referred to as "scrotal " The tongue may protrude but is not unusually large except in some cases in which hypertrophy may be present. Protrusion is due to the smallness of the oral cavity rather than the size of the tongue



fetus 15 mm (C) Postnatal

Voice

Of special interest is the voice. Many small mongoloid children have raucous, low-pitched voices which are almost masculine and in striking contrast to their infantile appearance. I have not been able to find a plausible explanation for this disorder. In studying the larynx of several subjects, I have found the mucosa thickened and fibrotic, and the larynx has seemed higher in the neck than usual. It is also possible that the absence of sinus formation in the skull has something to do with the deep voice and its lack of resonance

The same type of voice is common in cretinism The most likely explanation seems to be myxedema of the pharynx, since only a restricted number of mongoloids have such a voice and it disappears under thyroid treatment

Nose

The nose of the mongoloid is characterized by flatness of the nose bridge, owing to absence or underdevelopment of the nasion bone (figs. 6 and 7) The cartilaginous part

producing a

with broad

chae often

thickened, the air passages being narrow or almost obstructed (fig 13).

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TABLE 2.—*Dental Development*

Age in years	Sex	No of cases	Irregular alignment	Caries		Paradentosis	Retarded eruption	Missing teeth
				Moderate	Severe			
3–5	M	—	—	—	—	—	—	—
	F	5	4	—	0	5	5	0
6–10	M	10	9	6	0	7	1	1
	F	6	5	—	1	6	2	1
11–15	M	13	8	7	0	13	5	3 poss 4
	F	16	11	8	0	14	4	7
16–20	M	9	8	4	0	9	1	4
	F	7	5	5	0	7	1	4
21–30	M	7	4	4	0	7	4	2
	F	9	9	8	0	8	—	6
31–35	M	—	—	—	—	—	—	—
	F	2	2	2	0	2	—	1 (?)
		84	68	44	1	78	18	28 poss 30

Some aspects of the tooth development in mongolism have been the subject of a special study by Dr. John A. Nash, who examined several hundred mongoloid patients and registered his findings in 84 cases ranging in age from 3 to 35 years This study covered the following items· alignment, mucous membrane, caries, paradentosis and eruption of teeth The results, grouped according to age, are given in table 2 Certain points are worthy of special emphasis Abnormal alignment was seen in 68 cases, the majority having crowded conditions and a small number of widely spaced teeth. The most conspicuous fact is the absence of caries Moderate and very moderate caries were present in 44 cases, and 39 cases were completely free of caries; extensive caries was found in only one case of the whole group. This is the more striking considering the rather poor dental hygiene of these children even with close supervision, owing to their mental shortcomings Equally important is the frequency of paradentosis, which was found in at least 78 out of 84 cases. Gingivitis in differing degrees was local in 33 and general in 45 instances Pocket formation was present in 45 cases, recession in 59

Eruption of teeth ...
were missing in at lea...
possible to decide w... ...was merely a delay in eruption or
whether the teeth were compl...
in several insta...

It goes with



FIG 13—Horizontal section through nasal cavity of a mongoloid, age 12 years SE, nasal septum, C medial conchae, S maxillary sinuses, OS OCC. occipital bone The conchae are deviated, the mucosa greatly thickened The air passage is narrow and partially obstructed

Dental Development

Observations on the teeth are of special interest because they furnish some insight into the disturbance in bone formation. It has not escaped attention that the eruption of first teeth is usually retarded. Brousseau studied the exact time of appearance and found that eruption was rare before the ninth month whereas normal children have first incisors at six months of age A large number of mongoloids had their first teeth between the ages of 12 and 20 months There were a great many cases in which the first tooth appeared at the age of 2 years or later Dentition was usually not completed before the fourth or fifth year and frequently was even more delayed Eruption did not follow the usual pattern, the molars appearing before the incisors in many instances. The second dentition began somewhat more regularly but again was irregular and frequently incomplete.

The jaws are abnormal in size, the upper jaw being too small and the lower jaw showing prognathism. This is due to the absence of counteraction from the upper jaw under the stress of abnormal muscle pull. These anomalies of the jaws are not without influence upon the development and alignment of the teeth, which are crowded, the spacing is sometimes abnormally wide, and normal alignment is rare.

in the ablation or malformation of the permanent lateral incisor in the mongoloid

Further information with regard to dental development, collected in radiologic studies (by R. Spitzer and M. I. Robinson), will be found in Chapter IV.

Neck

The neck of the mongoloid is short and seems unusually broad, apparently because of the straightness of the vertebrae and the flatness of the occiput There may be great laxity of the skin.

Trunk

Although the trunk is relatively long in comparison to the shortness of the extremities, there are definite evidences of growth deficiency The chest appears round, but depression of the sternum is often seen. The spine does not show the normal curvature and has a tendency to straightness or dorsolumbar kyphosis

Abdomen

The abdomen is pear-shaped and distended, with insufficient muscle tone The liver is frequently palpable beneath the costal margin on account of the small chest and atonia of the abdominal muscles [illegible]

ar [illegible] observed. On the other hand, macrocolon or extreme distension of sectors of the small or large intestines is not rare Congenital stenosis of the large intestines has been reported, and pylorus stenosis is not unusual In acute conditions of abdominal distress, volvulus has to be considered.

Pelvis and Hips

Anomalies of the pelvic bones in mongoloids were noted by Caffey and Ross Their studies indicate anomalies of the acetabular and iliac angles as well as structural anomalies of the iliac wings The acetabular angle in normal individuals has a mean of 28 degrees with a range of 8 to 32 degrees for males and 14 to 44 degrees for females. On the other hand, the mean value for mongoloid cases was 15 degrees with a range of 4 to 20 degrees for the males and 4 to 30 degrees for the females The mean iliac angle for the controls was 55 degrees with a range of 44 to 74 degrees for both sexes, while the mongoloid cases had a mean of 45 degrees with a range of 35 to 50 degrees Caf-

mal and are frequently abnormally shaped, in addition to showing moderate hypoplasia. This growth deficiency is a part of the general growth disorder which I have already emphasized.

Dr. Nash's study reveals two factors hitherto unrecognized and of great biologic interest. Whereas other investigators have felt that mongoloid teeth are predisposed to caries, it has now been established that caries is rare even in the age group above 16 years, when most normal children have a considerable number of tooth caries. At the same time, paradentosis is present from the very beginning, and five girls below an age of 5 years showed a marked degree of paradentosis.

Periodontal disease has been the subject of a special study carried out by Dr M. Michael Cohen, who reports the following observations*.

One hundred male and female mongoloid patients, 3 to 27 years of age, were studied at the Walter E Fernald State School in Waltham, Massachusetts, for the prevalence of periodontal disturbances Color intraoral Kodachrome photographs were taken of each patient under standardized conditions Clinical examinations of occlusal relationships of jaws, size and number of teeth present, gingival and periodontal disturbances were recorded Intraoral radiographs were also taken Periodontal disease was observed clinically and roentgenographically in 95 per cent of the patients

Periodontal disturbances were observed in young mongoloids between the ages of 3–8 years Generalized chronic inflammatory gingival enlargement was present in the majority of these children Calculus, gingival recession as well as pocket formation were also noted Several patients in this age group had a premature exfoliation of the primary mandibular incisors and molars In the early mixed dentition in young mongoloids, ages 8–11 years, bone loss was observed roentgenographically in approximately 70 per cent of the patients Older mongoloids, 11–14 years of age, had exfoliated the mandibular permanent central incisors, and when the mandibular incisors were present, marked gingival recession mobility and bone loss were apparent clinically and radiographically

Of 100 mongoloids examined clinically and radiographically, 95 per cent manifested periodontal disease while 70 per cent showed a midline defect with marked bone loss in the mandibular incisor region

Another dental abnormality observed in this group was the absence or stunting of the maxillary and mandibular permanent lateral incisor Thirty-two patients had missing permanent lateral maxillary or mandibular incisors The maxillary lateral incisors were most frequently missing Nine patients manifested stunting of the permanent lateral incisor

Forty-one (41 per cent) mongoloid patients were found to have missing or stunted permanent lateral incisors The maxillary permanent lateral incisor lamina for the permanent tooth may be observed in the developing jaw bones at approximately the ninth week of fetal age. Critical stress at this period may result

* Personal communication This study was sponsored by the Public Health Service, United States Department of Health, Education, and Welfare, Bethesda, Md (Grant D-760)

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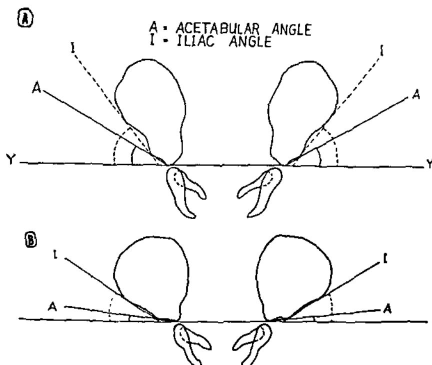


FIG 14—(*A*) Schematic drawing of the acetabular and iliac angles in the pelvis of the newborn. According to the method of Hilgenreiner, the Y-Y line is drawn through the lower edges of the Y cartilages The oblique line (A) is drawn through the lower and upper ends of the acetabular roof The iliac line (I) is drawn through two points the most lateral point of the iliac body below, and the most lateral point of the iliac wing above. (*B*) The acetabular and iliac angles in mongolism are much smaller than in normal controls Note also the flatness and width of the iliac wings (See Caffey and Ross Mongolism (Mongoloid deficiency during early infancy—some newly recognized diagnostic changes in the pelvic bones) Pediatrics *17* 642, 1956)

fey and Ross defined the iliac index as "the sum of both acetabular angles and both iliac angles divided by 2." The mean value of the iliac index at birth is 81 for normal infants, compared with the expected low value of 62 for infants with mongolism. The mean value for normal six month old infants is 79, against 51 for infants with mongolism. Caffey and Ross also call attention to the iliac wings, which seem large and flare laterad.

Genitalia

The male sex organs are retarded in development In about 50 per cent the testicles are not descended at the time of birth and never do descend Frequently only one is found in the scrotum, but even if both are descended, they are small and never of normal size. Though

they may appear of fairly good size on palpation, this does not indicate normal development. Fibrosis and fat tissue usually replace the parenchyma The penis is often infantile and short but may sometimes be long and thin Pubic hair is long and silky and of female distribution Axillary hair is absent. The secondary sex characters of mongoloids offer some indication of hermaphroditism. The breasts may show hypertrophy of fat, and the fat distribution of the abdomen is female If hair appears on the face, it is spotty and grows along the margin of the lower jaw. It is short, straight and silky, and does not resemble a normal beard

Female Sex Organs

The major labia in mongoloid infants are frequently oversized. Bleyer has reported this finding and considers the anomaly so characteristic that "it affords another sign " The skin is full and the labia form round cushions, whereas the minor labia are underdeveloped or absent They may be apron-like and protruding in older mongoloids The clitoris protrudes and is frequently hypertrophic Menarche is delayed about 70 per cent of mongoloid girls menstruate between the ages of 18 and 30 Menstruation is irregular, and menopause early The breasts remain infantile during puberty but later become



FIG 15 —Round, full labia in mongoloid female infant (Bleyer's sign)

large, owing to hypertrophic subcutaneous fat tissue. The nipples are frequently tiny and flat, and the glands of the areola may be missing. Adiposogenital dystrophy is present in many adult cases. Hirsutism is often marked.

Extremities

The extremities are short; the distal portions of the long bones of hands and feet are usually particularly affected. It is the growth deficiency of the facial bones, trunk and extremities in mongolism which leads to the term "acromicria." The fingers are short and in older persons often drum-shaped. The little finger shows a curvature in over 60 per cent of cases; the second phalanx of the little finger is often rudimentary or even missing. The thumb is shorter than normal and set at a lower position. The hands are flat, flabby and hypotonic. In newborns and infants, the skin is often wrinkled—like a glove which is too large—due to the general shortness of the bone structure.

The hand lines and dermatoglyphic patterns have attracted special attention among the many aspects of abnormal development in mongolism. A transverse palmar crease, also described as a "four finger line" or "macacus line," is often observed. In the average person, the hand lines follow standard patterns, as indicated by numbers and broken lines in figure 16*A*. In the mongoloid hand and in the hand of a certain percentage of normal people, lines 2 and 3 are united and form a transverse crease This "four finger line" starts at the radial margin and crosses the palm to the ulnar margin

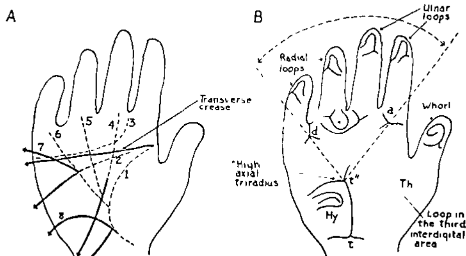


FIG. 16—Hand lines and dermatoglyphic patterns in mongolism (for detailed

As I said, the transverse crease occurs in a certain percentage of the normal population, apparently with great variation in different countries According to a Swiss study by Hans Erne, a transverse crease occurs in 1 per cent of the population and transitional forms in 1 to 5 per cent Among the mongoloids, this four finger line was found in 32 5 per cent of the cases in Switzerland and in 29 per cent in Italy; transitional forms were found in 7.5 and 9.5 per cent, respectively. This crease (F-2) reaches the ulnar margin of the hand in over 50 per cent of the mongoloid children. A study of the hands of relatives of mongoloid children revealed that 5.5 per cent showed transverse creases and 9 per cent transitional forms. Extension of the transverse crease to the ulnar margin was reported in 28 5 per cent of the relatives and in 23 5 per cent of the controls. Ulnar lateralization of F-2 depends, however, on the age of the person and becomes less conspicuous with advancing age. The transverse crease is said to reach the ulnar margin in more than 90 per cent of newborns.

As far as my own observations are concerned, the transverse crease in mongolism seems to differ somewhat from that seen in normal persons In the latter group, it is usually found to be bilateral. In mongolism, a unilateral transverse crease is almost twice as frequent as the bilateral one Table 3 records the condition of the hands in the last 60 cases of mongolism seen The table indicates that the unilateral four finger line is found more than twice as frequently on the left [illegible]

o

p [illegible] the left hand Similar observations were made by Féré, and Penrose states that the right hand is usually "the more mongoloid one"

In addition to the transverse crease or four finger line, which is easily recognized, the so-called "dermatoglyphics" (the epidermal ridges and their configurations) have attracted considerable interest. In 1939, H Cummins subjected the mongoloid hand to an extensive study with regard to the dermatoglyphics. Numerous investigators have followed and confirmed his observations The minute skin ridges of the hand, which form certain constant patterns that make

TABLE 3 —*Transverse Crease in 60 Mongoloids*

No of patients		None	Bilateral	Unilateral	
				Right	Left
Inpatient	45	22	8	5	10
Outpatient	15	1	3	2	9

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Extremities

The extremities are short; the distal portions of the long bones of hands and feet are usually particularly affected. It is the growth deficiency of the facial bones, trunk and extremities in mongolism which leads to the term "acromicria." The fingers are short and in older persons often drum-shaped. The little finger shows a curvature in over 60 per cent of cases; the second phalanx of the little finger is often rudimentary or even missing. The thumb is shorter than normal and set at a lower position. The hands are flat, flabby and hypotonic. In newborns and infants, the skin is often wrinkled—like a glove which is too large—due to the general shortness of the bone structure.

The hand lines and dermatoglyphic patterns have attracted special attention among the many aspects of abnormal development in mongolism. A transverse palmar crease, also described as a "four finger line" or "macacus line," is often observed. In the average person, the hand lines follow standard patterns, as indicated by numbers and broken lines in figure 16*A*. In the mongoloid hand and in the hand of a certain percentage of normal people, lines 2 and 3 are united and form a transverse crease. This "four finger line" starts at the radial margin and crosses the palm to the ulnar margin.

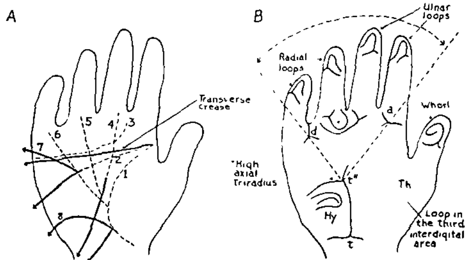


FIG. 16—Hand lines and dermatoglyphic patterns in mongolism (for detailed description, see text)

opinion. In our clinical material of more than 1,000 cases, there were less than a dozen in which there was any doubt as to the diagnosis. The study of dermatoglyphic configurations does not shed additional light on the diagnosis in dubious cases. The configurations in borderline cases are so indistinct that they can be interpreted in either direction Even in true cases of mongolism, only 70 per cent of the patients display a significant combination of patterns; and the patterns are either absent or inconclusive in the remaining 30 per cent. On the other hand, a combination of patterns similar to those found in mongolism is observed in over 20 per cent of the normal population without having any significance.

As to the scientific importance of the studies reported above, the slight increase in transverse creases as well as positive dermatoglyphic patterns has suggested a genetic implication to some investigators (Penrose, Hanhart, Erne)

The dermatoglyphic patterns in mongolism are an expression of a "primitive fetalization" (Cummins). The transverse crease is a manifestation of an abnormally long persistence of the embryonic mounts. The denseness and character of the dermatoglyphic patterns also indicate a fetal deceleration of development, similar to that which has been demonstrated in other organs Thus far, the dermatoglyphic patterns add more evidence to the concept of fetalization in mongolism. If a great frequency of similar patterns could be found in the mothers and siblings of children with mongolism, it would indicate that the maternal and sibling constitutions have a certain susceptibility to the noxious factors that can produce mongolism Since the abnormal patterns develop—as an expression of fetal retardation—in the same critical phase in which the other characteristics of mongolism are established, their presence does not contribute to an understanding of the noxious agent causing the fetalization and the time of onset of its operation

The *toes and feet* show patterns similar to those of the hands There is a large gap between the big toe and the second toe, and a deep line may extend from this gap to the sole of the foot. The third toe is frequently longer than the second toe, and two toes may be grouped together in a fork-like position. Webbing is sometimes present The foot is round and lacks the formation of an arch, and the sole shows many transverse wrinkles.

Skin

There is some disagreement [illegible]
skin, an[illegible] of the
thyroid [illegible] of the
[illegible] that the soft [illegible]

identification of individuals possible, often show characteristic deviations in mongolism. The patterns are laid down in the third and fourth fetal months and remain unchanged throughout life (Cummins, Bonnevie, Evatt).

Figure 16*B*, drawn after the publications of Penrose, Ford-Walker and Erne, illustrates some of the loops and whorls seen in mongolism. According to the statistics of Ford-Walker, loop patterns on the right palm have the greatest significance. In her material, they were present in mongoloids in 84.7 per cent whereas in 1000 controls they were found in 53.6 per cent.

Another subject of interest is the "triradius" (t) pattern to which Penrose called special attention. A triradius is defined as "the meeting place of three lines or spokes which make angles of 120 degrees with each other and demarcate the three regions" (Penrose) Unless each of the angles between the spokes is 90 degrees or more, no triradius is deemed to exist. Penrose introduced a system of measurements of the maximal *atd* angle which is formed by the lines drawn from *t''* toward *a* and toward *d* (fig 16*B*). Penrose concluded that the critical point is an angle of 56 to 57 degrees An angle greater than 57 degrees is found in the majority of mongoloids, while in normal individuals the angle is most often less than 56 degrees. From table 4 it is obvious that among the parents and siblings of mongoloids, a greater number (13 6 per cent) have a wider angle than among the controls, in whom an angle greater than 57 degrees was found in only 7 9 per cent. This difference, though small, is considered to be possibly of some significance.

These dermatoglyphic observations are of considerable theoretical interest Cummins, Ford-Walker and Penrose have also attributed some diagnostic importance to them, but I cannot concur in this

TABLE 4 —*Percentage Distribution of Measurement of Angle "atd" on Both Hands*
(According to Penrose)

"atd" angle (°)	Sex	Normals (%)	Mongoloids (%)	Parents (%)	Sibs (%)	All relatives (%)
<57	M	6 5	82 6	10 8	12 7	11 5
	F	9 2	85 0	14 2	15 9	15 0
	T	7 9	83 7	12 7	14 8	13 6
>56	M	93 5	17 4	89 2	87 3	88 5
	F	90 8	15 0	85 8	84 1	85 0
	T	92.1	16 3	87 3	85 2	86 4

anomalies may be found, such as abnormal distribution of the vessels, congenital pulmonary stenosis, aortic stenosis, open ductus botalli, and dextrocardia The variety of defects is great, and almost every mongoloid heart reveals at least one.

The deficiency of the vascular system is not restricted to the heart. The whole system is inadequate, narrow, and thin, and the peripheral capillaries are underdeveloped It never has been thoroughly investigated whether the hypoplasia of the vascular system forms an important link in the chain of functional inadequacy The vessels of the brain are thin and less numerous than in control cases, even of mentally deficient persons. The same is true for the endocrine organs and practically the whole body. The capillaries are found congested and enlarged—another symptom of significance. Some insight into the pathology can be gained by capillary microscopy, a method which is easily used and deserves a greater clinical application Studies in cretinism have provided evidence that in this condition hypoplastic capillaries are frequently found, developmental anomalies which point to the prenatal period The same is true for mongolism. Many mongoloids have abnormal capillaries Pototzky has utilized the experience gained in cretinism and thinks that one can distinguish between mongoloids with thyroid or pituitary deficiency and those without. However, in view of the pathologic material to be presented in a later chapter, Pototzky's conclusion seems to overshoot the goal I was not [illegible] statement, but the method is useful in diagnosis and rechecking of therapeutic progress, and deserves, therefore, more general application

Measurements

The growth process in the mongoloid child results finally in a stunted growth or dwarfism. The growth patterns are best demonstrated in figure 17, which gives the measurements of 175 outpatients and 73 ambulatory subjects that have undergone treatment.*

In analyzing figure 17, the following observations are pertinent:

In the age group from birth to 1 year, 66 per cent are [illegible]
and 26 per cent [illegible]
In the age grou[illegible]
and 66 per cent [illegible]

* This chart encompasses treated and untreated cases The specific effect of treatment will be analyzed in chapter XI

velvety skin of the mongoloid baby is distinctly different from the skin of the cretin. The subcutaneous tissue contains much fat and is puffy. The skin appears marmorated at the trunk and thighs because the capillaries are marked and congested. The skin of the cheeks is often strikingly red, this redness being sometimes circular or spotty and quite different from the color normally seen in children's cheeks.

As the mongoloid grows older, his skin rarely retains the characteristics described above. According to the degree of thyroid deficiency, the skin becomes thick, dry and rough, and various degrees of myxedema may be found The skin tends to be wrinkled and is susceptible to eczema.

Hair

The hair of the mongoloid is generally fine, silky and straight. Most mongoloids of mixed Anglo-Saxon stock have fair hair with definite lack of pigmentation. Those of Mediterranean stock have dark hair and more pigment, but it is noteworthy that they also show less pronounced characteristics than do those of northern races The hair becomes dry with increasing age, and partial or complete baldness is not rare. I have seen three Negro patients with mongolism whose hair was black, and rather strong and curly.

The absence of the apocrine glands and hair in the axilla has been reported by Shelley and Butterworth. Alopecia (baldness, partial or complete) is not rare in both sexes.

Heart

The most common anomaly of the heart is a congenital septum defect. With regard to the frequency of this anomaly, statistics vary because of the different material that has been accessible to various investigators Children with a severe septum defect are likely to die early, and if autopsy material of children's hospitals is examined, congenital heart defects may range as high as 75 per cent. If, however, survivors beyond the first decade are examined, a septum defect is found in about 25 per cent This defect is clearly audible, but it does not interfere with the activities of the child It is rare to see a mongoloid child suffer from acute heart failure, although during their frequent infectious diseases the heart may give reason for concern. Even more important than the septum defect is the general infantilism of the vascular system The aorta is thin and narrow, and all the main trunks are definitely undersized. One wonders how the mongoloid child can display so much activity. The peripheral vascular system appears distended and congested A great variety of other heart

anomalies may be found, such as abnormal distribution of the vessels, congenital pulmonary stenosis, aortic stenosis, open ductus botalli, and dextrocardia. The variety of defects is great, and almost every mongoloid heart reveals at least one.

The deficiency of the vascular system is not restricted to the heart. The whole system is inadequate, narrow, and thin, and the peripheral capillaries are underdeveloped. It never has been thoroughly investigated whether the hypoplasia of the vascular system forms an important link in the chain of functional inadequacy The vessels of the brain are thin and less numerous than in control cases, even of mentally deficient persons The same is true for the endocrine organs and practically the whole body. The capillaries are found congested and enlarged—another symptom of significance Some insight into the pathology can be gained b [illegible]

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Measurements

The growth process in the mongoloid child results finally in a stunted growth or dwarfism The growth patterns are best demonstrated in figure 17, which gives the measurements of 175 outpatients and 73 ambulatory subjects that have undergone treatment *

In analyzing figure 17, the following observations are pertinent·

In the age group from birth to 1 year, 66 per cent are within the normal range and 26 per cent are definitely below average

In the age group from 3 to 4 years, 32 per cent are within the normal range and 66 per cent below average

* This chart encompasses treated and untreated cases The specific effect of treatment will be analyzed in chapter XI

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The measurements show that the mongoloid newborn is often slightly shorter than average, measuring between 18 and 20 inches *(46 to 51 cm.)* in length. The weight varies greatly, underweight as well as overweight being observed. It must be taken into consideration that a high percentage of mongoloid babies are premature.

A relatively higher percentage of children with mongolism appear to be within the normal range if compared with a standard measure. ... the actual height, mongol- ... erweight. ... that growth slows down with increasing age and reaches an early standstill. At the end of the growth period, few persons with mongolism exceed a length of 5 feet (150 cm.) In 368 observations, only 14 boys and one girl reached a height of over 5 feet.

There is no close correlation between the early growth rate and the height reached at adulthood. Some children who seem to grow fairly adequately early in infancy reach a final height of not more than 4 feet. Other children who seem very much retarded in early childhood show a greater growth rate in their early teens.

In mongolism, growth at the distal ends of the long bones is insufficient, resulting in a shortening of the femur and humerus; but even more pronounced is the growth deficiency toward the distal ends of all extremities, that is, hands, fingers, feet and toes. Each bone shows increasing hypoplasia the more peripheral it is. Each center seems to be laid out fairly normally, but since growth proceeds in the periphery, away from the center, we see a true "acromicria" (*acros*—end, point, *micros*—small)

... ficiency is a "hypomorphy" (Davenport) with a well defined pathology in which the growth of the distal parts is predominantly involved, giving rise to what I comprehend in the term "acromicria." The difference between a mongoloid and a normal premature baby is that the latter is proportionate in its features according to the stage of development which it has reached at the time of birth. The mongoloid is not proportionate, it shows a "rounding" of the features because of delay of distal growth.

There are degrees of growth deficiency. It is not infrequently stated in the literature that mongolism is either present or not, that no gradations of mongolism are to be found. Fanconi emphasized this idea by stating, "There are no transitional forms between mongolism

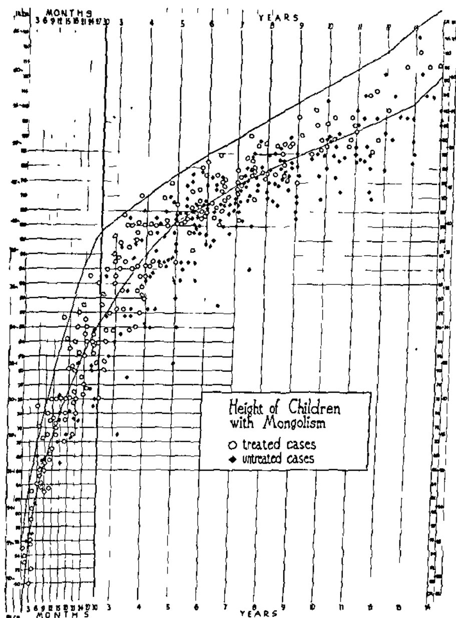


FIG 17 —Height of 73 patients (*white circles*) who have undergone treatment, and 175 untreated outpatients (*solid squares*) Solid lines indicate normal range (established by H C Stuart, Harvard School of Public Health) Note striking retardation in growth of the untreated mongoloid child (For details see text, page 39, and chapter XI, page 245)

In the age group from 10 to 11 years, 20 per cent are within the normal range and 72 per cent below average

In the age group from 12 to 18 years, 20 per cent are within the normal range and 73 per cent are below normal

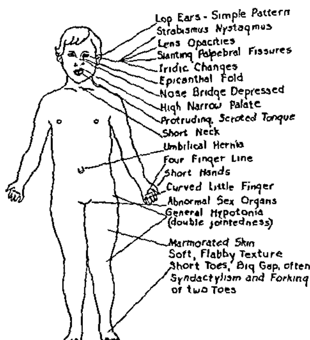
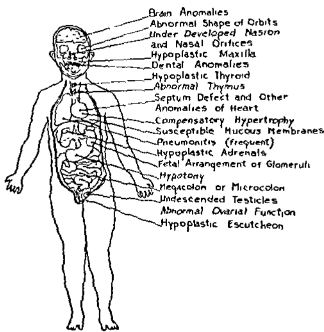


FIG 19 —Variety of external characteristics found in mongolism



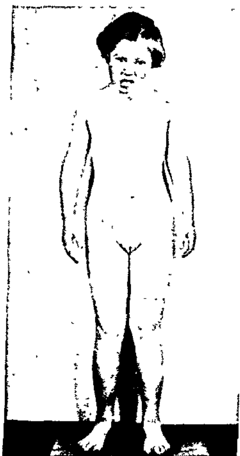


FIG 18—General infantilism in mongolism Mongoloid girl almost 15 *years of age, height 52 inches,* developmental age 9 years, developmental quotient about 60 per cent Note length of trunk and shortness of neck, arms and legs, especially feet, gap between big toe and second toe, marked marmoration of skin of thighs and lower legs, shortness of hands, breasts still completely un*developed; no pubic or axillary hair.*

and the normal " However, there are gradations, and mongolism is not a malformation or pathologic mutation of a definite degree.

After birth the abnormal features of the mongoloid child become more conspicuous with each passing week. In some cases it may, therefore, be well advised to refrain from judgment until several weeks have elapsed, when the diagnosis can be established without doubt. The fact that mongolism becomes more conspicuous is not due to an increasing development of the pathologic features, but to lack of normal development. Everyone familiar with the growth of infants knows the amount of development that takes place immediately after birth and continues for the first two years The appearance of a baby changes with every passing week In the mongoloid this process of molding is absent or strikingly delayed, and the unfinished appearance of these patients becomes, therefore, increasingly more evident.

I have described the physical characteristics which are present in every case to a greater or lesser degree. Mongolism is also frequently associated with a number of other malformations which have to be

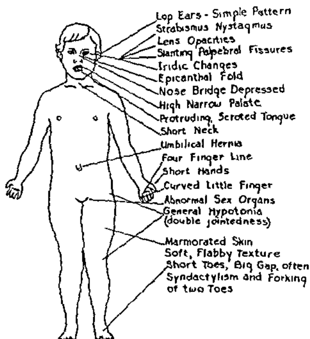


FIG 19 —Variety of external characteristics found in mongolism

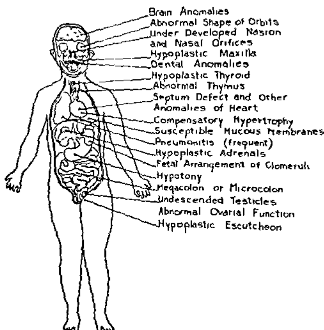


FIG 20 —Variety of internal anomalies in mongolism

taken into consideration when the prognosis is discussed. The malformations indicate abnormal fetal development of a more severe degree than is present in the average mongoloid. The more malformations are found, the less promising is any therapeutic effort.

Almost every type of malformation has been observed in mongolism, and it is of little value to report each single case. In the following I list the more frequent anomalies which may be found in addition to features discussed before:

Cataracta zonularis, polaris anterior, centralis
Ectopia lentis
Coloboma lentis
Panophthalmia
Optic atrophy, deficiency in myelination
Exophthalmos
Occlusion of external ear
Septum defects of nose
Hydrocephalus (rare), possibly due to rickets
Congenital clubfoot, hemiplegia, paraplegia
Syndactyly of fingers or toes, fork position, irregular length of toes
Heart Defects of intra-auricular septum, patent foramen ovale, intraventricular septum defects, pulmonary stenosis, Fallot's tetralogy (pulmonary stenosis, defective intraventricular septum, *hypertrophy of right ventricle, dextroposition* of aorta), patent ductus arteriosus botalli
Umbilical hernia, diastasis of abdominal muscles, splanchnomicria, microcolon, colon stenosis
Hypospadia, undescended testicles, fimosis, infantilism, hypertrophy of clitoris, absent minor labia, long, apron-like labia, hypoplasia of uterus

CHAPTER IV

ANATOMIC AND X-RAY OBSERVATIONS

ANATOMIC OBSERVATIONS

The Head in Mongolism

Figure 21 tabulates measurements of the normal circumference of the skull and the circumference of 125 mongoloid children. Three points shall be stressed in considering the normal growth of the skull First, there is a remarkable increase during the first year of life, during which the head gains more than 10 cm in circumference Second, there is a steady, but slower, increase in size during the next 5 years of life, and third, there is a new impulse of growth after about the twelfth year.

Anatomists are of the opinion that the last period of growth of the skull does not greatly increase the brain cavity but does increase the size of the skull through development of the sinus system, especially of the frontal sinus, through the development of the diploe of the skull and through periosteal proliferation

In the mongoloid skull, there is a marked difference from the normal development At birth the circumference is for the most part within normal limits Only a few mongoloids show measurements which are definitely below the normal. After birth, in the first few months of life, the mongoloid skull shows a remarkable retardation in growth At the age of 1 year the skull does not even reach the size of that of a normal 6 months old child, and at the age of 2 years the mongoloid skull corresponds to that of a 9 month old child The most impressive fact is that mongoloid children need almost 9 years to reach the level of a normal 1 year old baby The mongoloid skull stops growth at an age of about 14 years, reaching a circumference corresponding to that of normal children between 3 and 4 years old.

Figure 22 gives more details in regard to the growth disorder of the skull It is obvious that the failure in development is due to a marked lack of growth in length

The width of the skull is slightly below the normal. The high cephalic index is therefore not due to a real broadening of the skull but to the failure of growth in length

A better understanding of the growth disorder will be reached by comparing it with the normal development from birth to adult life. To a great extent, anatomists have dwelled upon the changes of the normal skull which occur during the period of development and which are persistent in spite of the encountered variations of familial and racial appearance. In studying skulls, one places the specimen in such a position that the so-called "base-line" or Frankfurter horizontal (a line which runs through the inferior margin of the orbit hole and the superior margin of the external auditory meatus) is in a horizontal position. A perpendicular line is drawn through the alveolar process in front of the face. The skull of the newborn infant differs from that of the adult in several points, and it may be useful to mention a few measurements and proportions which are of importance for the understanding of normal development as well as of the mongoloid growth disorder. Most outstanding in the newborn

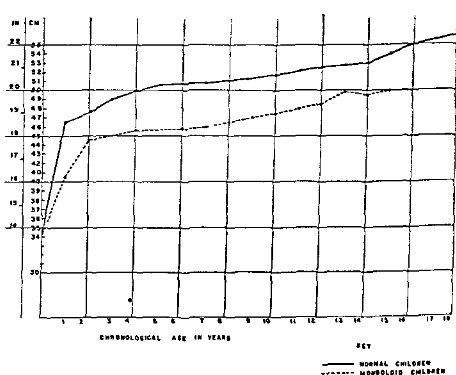


FIG. 21 —Circumference of skull, normal development and in mongolism. The straight line represents standard values, the dotted line observations on 125 cases of mongolism. Note the great delay of skull expansion in the first year, at 1 year the skull circumference of the mongoloid baby hardly equals that of a 6 months old child and at 2 years the skull circumference corresponds to that of a 9 months old baby. After that time the skull expands slowly and lags about 2 inches behind the normal.

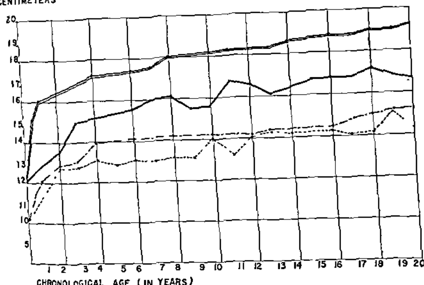


Fig 22—Length and width of skull, normal standards and in mongolism The two lines represent normal standards In mongolism growth of the skull in length is exceptionally deficient, resulting in extreme brachycephaly The width of the skull is relatively better developed but remains below normal

skull are the large brain cavity and the small face Average length, measured from the glabella to the occipital point, is 11 5 to 12 cm, average parietal width (bip.), 9 5 cm. The circumference of the skull is 34 cm, or 13 5 inches In studying the proportions of the face, it is noteworthy that the vertical distance from the vertex to the nasion is twice as large as that from the latter to the alveolar point The orbital holes appear disproportionately large in the newborn infant, and in comparing the height of the orbital hole with the distance from the lower orbital margin to the alveolar crest one will recognize that the latter distance measures less than the orbital height The distance from the anterior nasal spine (acanthion) to the alveolar point (prosthion) is short but large enough to provide adequate berth for the developing upper teeth A last item of interest is the position of the transverse axis of the atlanto-occipital joint. According to Froriep, in the newborn infant it is in the middle of the base line, the proportion between the anterior and posterior sections being 3:3 Growth of the

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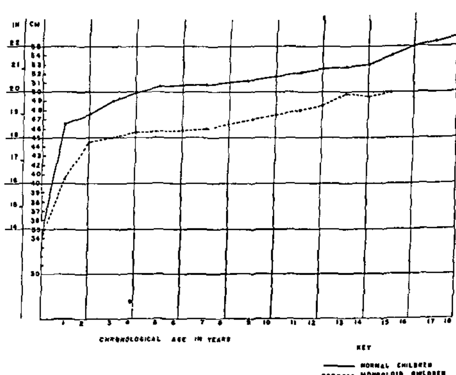


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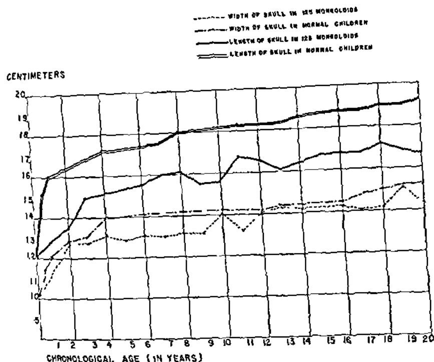


Fig 22 —

skull are the large brain cavity and the small face. Average length, measured from the glabella to the occipital point, is 11.5 to 12 cm., average parietal width (bip), 9 5 cm. The circumference of the skull is 34 cm , or 13 5 inches In studying the proportions of the face, it is noteworthy that the vertical distance from the vertex to the nasion is twice as large as that from the latter to the alveolar point. The orbital ... newborn infant, and in ... the distance from the ... will recognize that the ... distance measures less than the orbital height. The distance from the anterior nasal spine (acanthion) to the alveolar point (prosthion) is short but large enough to provide adequate berth for the developing upper teeth A last item of interest is the position of the transverse axis of the atlanto-occipital joint ... the ... be ...

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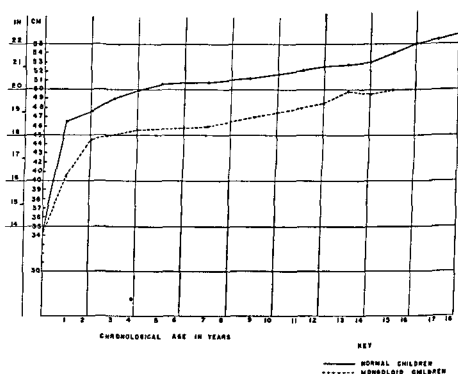


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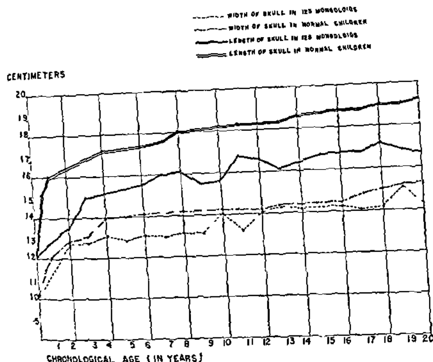


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A better understanding of the growth disorder will be reached by comparing it with the normal development from birth to adult life. To a great extent, anatomists have dwelled upon the changes of the normal skull which occur during the period of development and which are persistent in spite of the encountered variations of familial and racial appearance In studying skulls, one places the specimen in such a position that the so-called "base-line" or Frankfurter horizontal (a line which runs through the inferior margin of the orbit hole and the superior margin of the external auditory meatus) is in a horizontal *position. A perpendicular line is drawn through the* alveolar process in front of the face. The skull of the newborn infant differs from that of the adult in several points, and it may be useful to mention a few measurements and proportions which are of importance for the understanding of normal development as well as of the mongoloid growth disorder. Most outstanding in the newborn

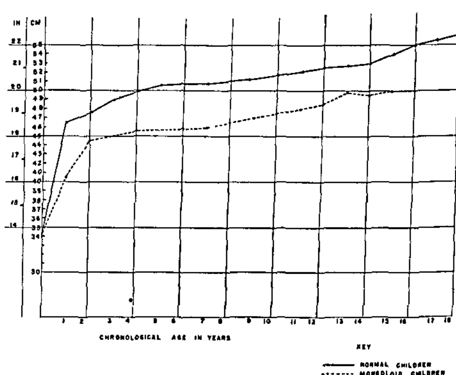
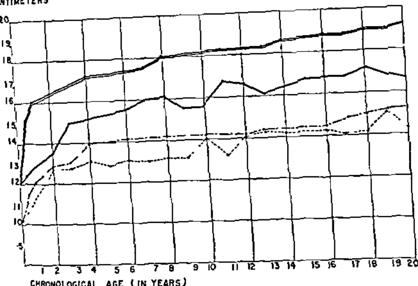


Fig. 21 —Circumference of skull, normal development and in mongolism. The

the normal



skull is relatively better developed but remains below normal

skull are the large brain cavity and the small face Average length, measured from the glabella to the occipital point, is 11 5 to 12 cm , average parietal width (bip.), 9 5 cm. The circumference of the skull is 34 cm , or 13 5 inches. In studying the proportions of the face, it is noteworthy that the vertical distance from the vertex to the nasion is twice as large as that from the latter to the alveolar point The orbital holes appear disproportionately large in the newborn infant, and in comparing the height of the orbital hole with the distance from the lower orbital margin to the alveolar crest one will recognize that the latter distance measures less than the orbital height. The distance from the anterior nasal spine (acanthion) to the alveolar point (prosthion) is short but large enough to provide adequate berth for the developing upper teeth. A last item of interest is the position of the transverse axis of the atlanto-occipital joint. According to Froriep, in the newborn infant it is in the middle of the base line, the proportion between the anterior and posterior sections being 3:3. Growth of the

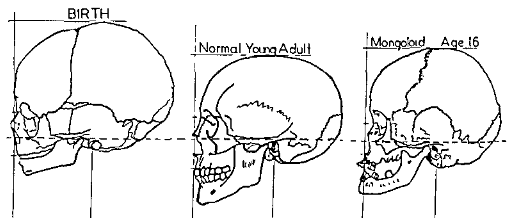


FIG 23.—Comparison between normal skull and mongoloid skull The configuration of the skull (*A*) at birth, (*B*) in a young adult, and (*C*) in a mongoloid Note the large brain cavity and the small face at birth. The distance from the bregma to the nasal root measures twice the length from the nasal root to the alveolar crest Note the short distance from the nasal spine and the inferior orbit margin to the alveolar crest Note shape of infantile mandible The transverse axis of the atlanto-occipital joint is in the middle of the base line

The outstanding feature in the young adult is the increase in size of the facial bones The lower margin of the orbit hole is far apart from the alveolar crest The mandible shows angulation.

The mongoloid skull preserves the fetal proportions although some increase in size is noticeable The face remains small. The nasion and maxilla are underdeveloped, and the mandible shows fetal shape. The transverse axis of the atlanto-occipital joint is still in the middle of the base line, or sometimes even nearer to the front line.

skull base displaces the site of the atlanto-occipital joint backward The proportion in a 10 year old child is about 4.3, and in adult life, 5.3. The development of the musculature of the neck counteracts the nodding of the head forward in upright position which takes place if man falls asleep In the child the head is balanced. During the extensive growth which is going on in the first year of life, the circumference of the skull increases 3 to 4 inches, or 10 cm, the circumference of the head at 1 year being 42 to 44 cm In the fifth year of life, the circumference usually reaches 50 cm, or 20 inches These measurements are of importance because during infancy the skull bones are thin and the sinus system not yet developed The circumference offers, therefore, a fair estimate of the brain cavity and the size of the growing brain The increase of the size of the skull is produced by growth of the skull base in the lines of the cartilaginous and membranous synchondroses and by osseous proliferation about the margins of the flat skull bones, the sutures acting like the epiphy-

seal lines of the long bones Even more impressive than the increase of the brain cavity is the growth of the facial bones in postnatal life. The distance from the nasal spine to the alveolar crest increases rapidly; the lower orbit margin moves farther and farther apart from the alveolar crest, while the orbit holes gain very little in size. In the adult skull, the distance from the nasion to the alveolar point is equal to the height of the forehead. The mandible increases in size and the mandibular angulation becomes more marked

Comparison of the mongoloid skull with the normal development demonstrates impressiv

mer To speak of "the"

striking resemblance ir

alike these skulls are to each other, superimposition of their outlines conclusively demonstrates whether the orientation be lateral or facial. Nor is there any reason to believe that increased age would have altered their main characteristic" This is well demonstrated by Greig, who superimposed the outlines of three mongoloid skulls In figure 23 I have outlined one mongoloid skull which demonstrates well the whole pathology The transverse axis of the atlanto-occipital joint is still in the middle of the base line, in spite of the notorious brachycephaly of the mongoloid skull This is due to the extreme shortness of the skull basis in mongolism A second factor is the failure of growth of the maxilla and the nasal portion The proportion between forehead and face is still fetal. The deficiency of development of the maxilla places the lower margin of the orbit near the alveolar crest and the distance from the nasal spine to the alveolar point is as short as in a normal newborn baby The incisor teeth have no space for their roots and protrude. The angulation of the mandible is flat and definitely fetal in shape, but its outline is somewhat confused by the fact that the mental process is protruding and the anterior branch is bent This feature appears to me to be due to the fact that on account of the underdevelopment of the maxilla and the teeth, the mandible does not find the normal counteraction The strong muscle pull bends the anterior rami of the mandible upward

In summarizing the abnormality of the facial development of the mongoloid skull, it appears striking that the mongoloid skull is deficient in growth of all those structures which show the most marked development after birth, the nasal bone, ethmoid and maxilla, resulting in a persistence of fetal proportions of the face The outline of the mandible is sometimes confused in later life through protrusion, and prognathism occurs owing to muscle traction of the masticatory apparatus, but these secondary changes do not influence

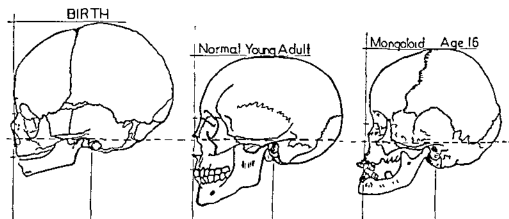


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skull base displaces the site of the atlanto-occipital joint backward. The proportion in a 10 year old child is about 4 : 3, and in adult life, 5 : 3. The development of the musculature of the neck counteracts the nodding of the head forward in upright position which takes place if man falls asleep. In the child the head is balanced During the extensive growth which is going on in the first year of life, the circumference of the skull increases 3 to 4 inches, or 10 cm., the circumference of the head at 1 year being 42 to 44 cm. In the fifth year of life, the circumference usually reaches 50 cm , or 20 inches These measurements are of importance because during infancy the skull bones are thin and the sinus system not yet developed The circumference offers, therefore, a fair estimate of the brain cavity and the size of the growing brain. The increase of the size of the skull is produced by growth of the skull base in the lines of the cartilaginous and membranous synchondroses and by osseous proliferation about the margins of the flat skull bones, the sutures acting like the epiphy-

the essential feature of mongolism, which consists in the failure of development of the protruding structures, the summits of the face. The micrognathic deficiency is only a part of the picture. The skull basis remains short on account of the insufficient growth of the synchondroses spheno-occipitalis and spheno-ethmoidalis Another factor which contributes to the shortness of the skull base is the absence of development of the frontal and sphenoid sinus. A brief glance over the picture of a transverse section through the normal skull reveals how definitely the sinus expansion influences the skull shape By eliminating the sinus system from the skull, one obtains the true outline of a sagittal section through the mongoloid skull (fig. 24). Another factor is the failure of the flat skull bones to produce sufficient growth at the bone margins. This failure is indicated clinically by the slow closure of the fontanels, which remain patent for several years It is also indicated by the remainder of sutures which disappear normally shortly after birth (frontal suture and sagittal suture) and the creviced sutures at the skull basis which were found by Greig A last item worth mentioning is the thinness of the flat skull bones owing to failure of diploe development. In my autopsy material, the skull bones measured 3 to 4 mm only instead of 6 to 10 mm, except in a few cases in which marked brain atrophy had increased internal bone proliferation The mongoloid skull is extremely light, and the skull bones are sometimes paper-thin, with irregular foramina where ossification is wanting

Ossification

If we compare histologically the three disorders [illegible]

[illegible] is absorbed early and replaced by ossified tissue In cretinism, growth of the bones of the skull is delayed because of lack of transformation of cartilage into bony tissue The cartilaginous spaces in cretinism are open much longer than is normal.

In mongolism, another aspect of ossification manifests itself. The synchondrosis spheno-ethmoidalis, in contrast to the synchondrosis spheno-occipitalis, consists of fibrous tissue. It undergoes ossification according to the process which unites the sutures of the skull and os-

FIG 21 (Continued) — The sphenoid sinus is missing and the [illegible] hypoplastic This [illegible] and sphenoid is [illegible] infantile forehead [illegible] plane than norm[illegible] sence of diploe formation of the flat skull bones [illegible] of maxilla and ab-

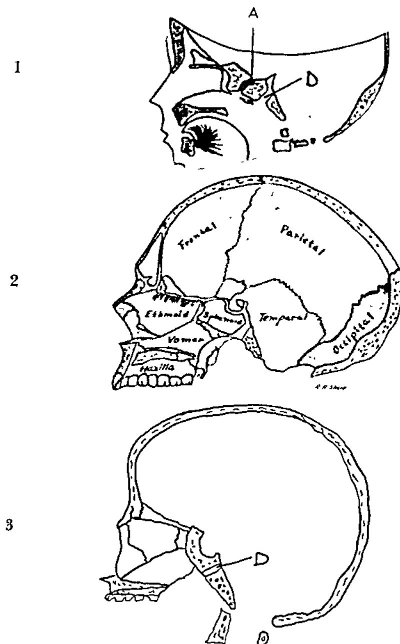


Fig 24—Skull diagrams, normal and in mongolism (1) Diagram of a skull of a year old child after Virchow Note cartilaginous disk between clivus and sphenoid body (D) and cartilage separating the sphenoid body (A) During development the anterior part of the sphenoid body moves downward and resumes a more horizontal position. Note site of future sphenoid sinus and frontal sinus. (2) Diagram of a normal adult skull. Note large size of sphenoid sinus and frontal sinus, and note influence of these sinuses upon configuration of skull and face (3) Diagram of a mongoloid skull

(Legend continued on facing page)

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Ossification

If we compare histologically the three disorders, chondrodysplasia, cretinism and mongolism, we may say that in chondrodysplasia growth of the base of the skull is arrested because of lack of development of the cartilage, which is absorbed early and replaced by ossified tissue. In cretinism, growth of the bones of the skull is delayed because of lack of transformation of cartilage into bony tissue. The cartilaginous spaces in cretinism are open much longer than is normal.

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Fig. 24 (Continued)—The sphenoid sinus is missing and the sphenoid body hypoplastic This body appears upright, and normal angulation between clivus and sphenoid is missing. *Note absence of frontal sinus*, resulting in a straight, infantile forehead The whole *anterior cavity is* shorter, steeper and on a higher plane than normal Note retraction of nasion, hypoplasia of maxilla and absence of diploe formation *of the* flat skull bones.

sifies the membranous bones. In a mongoloid boy of 9 years and 8 months, the anterior clinoid process was found far apart from the dorsum sellae and no ossification was taking place. Only the edges of the synchondrosis and of the anterior clinoid process were heavily ossified It is of interest that this synchondrosis formed a fibrous tongue protruding into the sphenoid body In another specimen from a 15 year old mongoloid child the synchondrosis spheno-ethmoidalis was also wide apart, without signs of ossification. This fact is of interest because Timme described the shape of the sella turcica in mongolism and noticed a peculiar appearance of the anterior part of the sella by x-ray examination. The same observation was later recorded by Tumpeer. Timme interpreted this change to be the result of enlargement of the pituitary gland Microscopic examination, however, shows that the radiographic appearance is due to the wide open synchondrosis and that *the shape of the sella is independent of the size of the pituitary* gland in mongolism. Moreover, the appearance of the sella turcica in mongolism corresponds to the x-ray appearance of a full term embryo in which the sella turcica also is separated into two sections.

In 1916, Stoccada published a paper on the synchondrosis spheno-occipitalis, its normal development and the alterations occurring in cretinism In this paper he described the synchondrosis at the time of birth, during the first decade, the second decade and after further growth had ceased My observations on control cases are in accordance with those of Stoccada. It may, therefore, be worth while to record a few points of interest concerning the development of the synchondrosis The cartilage which lies between the occiput and the sphenoid bone does not form a simple disk at the time of birth but continues to develop toward the posterior clinoid process as a cartilage slide of the same size as the disk, forming the rostral dorsum of the clivus blumenbachii and the posterior clinoid process. The cartilage disk of the synchondrosis averages from 3 to 3.5 mm in thickness. The cartilage cells form vertical columns in the center and are arranged in horizontal columns toward the occipital bone and the sphenoid body. *Growth occurs in two directions. The cartilage disk grows in* a vertical direction and the height of the disk increases steadily from about 7 mm. at birth to between 13 and 15 mm. at the age of 17 years The horizontal cartilage columns proliferate in the same manner as the epiphyseal lines of the long bones The thickness of the cartilage disk is about 3 mm. and remains this size for almost the first 20 years of life. At about the age of 20 years the cartilage becomes gradually absorbed and disappears. According to Stoccada the area of proliferation measures between 200 and 300 μ and the area of ossification

hat seen in the ribs
be mentioned that
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t year the cartilage
frequency shows a tongue-like protrusion into the sphenoid body. Therefore, the synchondrosis appears F-shaped. This cartilage tongue was found regularly in my material

Although the histologic appearance of the cartilage in cretinism and mongolism appears to be somewhat similar at first sight, there are marked differences if observed in more detail In cretinism the cartilaginous border of bone forms a straight line with few or no primary medullary cavities The ridge of ossification is rather thin The preparatory columns show a normal appearance; the cartilage, however, degenerates when lack of thyroid is not corrected by therapy or is experimentally produced by complete thyroidectomy. According to Stoccada, this is easily recognizable; the marrow cavities are rare, irregular in shape and separated from the cartilage by a ridge of bone. The disorder of ossification causes a persistence of cartilage Siegert and Stoccada interpreted the lack of ossification as being due to a deficiency of the bone marrow, which is not able to absorb the carti-
la...

a...

b...

a... ...cification of the spongiosa is not delayed There are a number of medullary cavities. The border of the bone is arcade-shaped Lack of proliferation of cartilage is easily recognizable. The cartilage disks are extremely small, and proliferation and formation of preparatory columns are arrested.

These observations are in accord with Lauche's studies of metatarsal bones His cases 1 and 4, mongoloid children aged 4 and 18 months respectively, showed a complete lack of cartilaginous proliferation. The cartilage was found to be covered with a more or less thick ridge of bony tissue which separated the cartilage from enlarged marrow cavities. In cases 2 and 3, children 10 and 12 months old respectively, slight traces of cartilaginous proliferation were still recognizable The bony tissue formed transverse ridges parallel to the cartilage border, which caused the formation of small secondary marrow spaces Lauche pointed out that in normal children growth goes on during the ossification period, except in the ...
cartilage ...
rested.

Kasow ... ...spaces were not finger-like proc-

esses, but occurred in the form of rounded, knob-like projections into the zone of cell columns, and that consequently the spongy bone did not consist of long tracts of bone but rather of rounded cavities.

The few studies of the growth of bone in mongolism are well in accord when the same bone structure is concerned. It is the distal and *not the proximal epiphyseal lines that are noteworthy. Moreover, one* has to bear in mind that growth in mongolism is somewhat irregular and periods of retardation may be followed by periods of more active growth.

The facts presented above—especially the more regular appearance of the centers of ossification, but delay of further growth, the small size of the cartilage disks, and the general growth disorder involving not only the cartilaginous epiphyseal lines but the membranous bones of the skull—indicate that the growth disorder is definitely different from that of cretinism. If the arrest of growth were restricted to the skull, the simplest explanation would be that the lack of development of the brain is the cause of the lack of further development of the skull. Such an explanation is correct for many forms of microcephaly in which the growth of the brain is arrested while the growth of the body continues undisturbed Although it is true that many microcephalic patients remain dwarfs and that general endocrine deficiency is frequently associated with microcephaly, the arrest of growth of the brain and of the skull precedes the arrest of the growth of the body for many years Microcephalic patients show a striking disproportion between circumference of the skull and the rest of the body, and observations prove that these patients grow at a normal rate during the first years of life while the skull remains undersized Not until several years of life have passed does the growth disorder of the body become apparent. The fact, however, that in later life microcephaly is frequently associated with a general endocrine disorder indicates an influence of the brain on the endocrine glands. In mongolism measurements and studies of brain development indicate that during the first half year of life the weight of the brain corresponds to normal, while at the same time a general growth disorder of the skull and the long bones is recognizable. The arrest of differentiation and the absence of growth stimulation apparently parallel the arrest of further development of the brain but do not depend on it. Moreover, the alterations of the vertebrae and of the long bones are independent of the brain and develop at the same time that arrest of growth of the skull occurs.

X-RAY OBSERVATIONS

The value of x-ray studies for the recognition of hypothyroidism rests upon the fact that the centers of ossification appear successively

over a period of about 14 years. The union of epiphyseal lines of the various bones is spread over a period of more than 25 years Since the calendar of ossification from birth to adulthood is well established, x rays offer an unparalleled opportunity to check on the progress of osseous development throughout life. The determination of the "bone age" is a standard method for the recognition of thyroid diseases.

Unfortunately very little use of radiologic studies has been made in mongolism, in spite of the fact that x-ray examination is not only extremely useful for the definite diagnosis of mongolism, but is also helpful for the evaluation of the condition and for periodic checkups of cases under treatment. In 1922 Willian Clift presented a thorough study of roentgenologic findings in mongolism which confirmed his opinion that the x-ray appearance of the mongoloid's osseous system represents the opposite of acromegaly.

Earlier investigators placed emphasis upon an x-ray study of the *sella turcica* The outline of the sella is, however, not abnormal in mongolism (Gordon, Bell, Benda) Pancoast, Pendergrass and Schaeffer in their book *The Head and Neck in Roentgen Diagnosis* refer only to Schuller, and mention that "the sutures and fontanelles are abnormally long in closing, and may remain open from three to five years after birth Schuller states further that *round defects may* occur in the suture lines"

The only newer x-ray study on some aspects of mongolism was made by Spitzer and Robinson They found that in mongoloids,

> both maxilla and mandible were under-developed along with the generally retarded growth The *mandibular* angle was obtuse, the ascending rami short and the horizontal part lacked *vertical height* In a number of cases delayed growth of the facial skeleton and *proportional maxillary* [illegible]
>
> [illegible] teeth, malformation of shape and size in the permanent dentition were characteristic features in Mongols Two distinctive types of lesion were *seen, microdontia* and malformations of shape resulting in haplodont, stunted teeth Both affections were always symmetrical in both upper and lower jaws, but *varying in* degree in the different groups The alveolar ridge was short and the mandibular [illegible]
>
> [illegible] delayed.
>
> [illegible] radiographs *conveyed* the appearance *of a* dysharmonic growth and of an *immature* dental system Evidence of *congenital* aplasia of one or even of two groups of teeth was obtained in 21 out of 28 cases in addition five cases showed *unilateral* anodontia Only two patients in this group had no congenital absence of any tooth group
>
> The eruption *of the* permanent dentition was delayed in 18 cases The *delay*

esses, but occurred in the form of rounded, knob-like projections into the zone of cell columns, and that consequently the spongy bone did not consist of long tracts of bone but rather of rounded cavities.

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Frontal bone
Anterior Fontanelle
Parietal bone
Angle of Mandible
Hypophyseal fossa
Atlas
Condylar part of occipital bone
(overlapping supra-occipital part)

Fig. [illegible].—X rays of normal skull and mongoloid shortly after birth. (*A, at top*) Lateral view of full term fetus after Cunningham's *Textbook of Anatomy*. Note size and angulation of sphenoid body and plane of cribriform plate. Note development of nasion and maxilla. (*B, at bottom*) X ray of 5 week old mongoloid baby representative of the whole group. Note abnorm[illegible] and small size [illegible] nasion and [illegible] at the same plane [illegible] instead of the skull basis. Note thinness of flat skull bones.

was not uniform and considerable variations occurred from case to case. It is of particular interest that two Mongolian sisters both had similar lesions in the teeth and skull

The characteristic changes of the dentition consisting of partial anodontia, mal-shaped teeth and delayed eruption, in several of the Mongolian patients were similar to those observed in the very rare, ectodermal dysplasia and in cranioc1eidodysostosis. Not one of the patients investigated showed precocious dental development

In turning attention to the proportions and the angulation of the skull base and face, x-ray pictures of the mongoloid skull are of indispensable value for an understanding of the anatomy. One x-ray picture will demonstrate the essential items better than the description of many skulls (fig. 25). It is obvious that the sphenoid body is smaller than normal and, most important, its position is more upright. The distance from the anterior clinoid process to the acanthion is shorter than normal, and the plane of the cribriform plate is displaced to a higher level. The *smallness of the maxilla is remarkable.* The nasal spine is close to the alveolar ridge, and the ridge appears on the same level as the sella instead of being on the same plane with the skull base. The axis of the atlanto-occipital joint is nearer to the face line than to the occiput, indicating the smallness of the bones forming the skull basis and the facial scaffolding.

Another item is the condition of the skull sutures. All sutures may *be separated, and one may find that the sagittal suture is not in approximation* and the parietal bones are separated ½ cm. or more. The frontal suture, which normally disappears within a few days after birth, may be found open even several months to years after birth. The same delay is recognizable about the lateral fontanel and those sutures which cross the sides of the skull.

It is noteworthy that the lateral view does not always reveal brachy*cephaly in infants. Later in life, brachycephaly is a persistent feature.* The position of the sphenoid body remains abnormal throughout life. Sinus formation is absent, and the sphenoid body remains small.

The confusing features of the anterior cavity are better understood when compared with anatomic observations made at autopsy.

The anterior cavity in cases of mongolism is characterized by the extreme protrusion of the roofs of the orbits. Slight projection of the roofs is normally observed, but in patients with mongolism they form a marked protuberance. The cribriform bone is short and retracted and forms a small, deep valley between the arches of the orbits. Another peculiarity of the roofs of the orbits is that they ascend laterally toward the frontal bone *without leaving any deepening between the* top and the facies temporalis of the frontal squama. This gives the

anterior cavity as a whole a curved shape, the floor sloping upward anteriorly and laterally toward the frontal bone. The sphenoid bone is small and the body of the bone underdeveloped. It is noteworthy that neither the frontal nor a sphenoid sinus is to be seen in cases of mongolism. Although these sinuses are not fully developed before the seventh year of life, slight pneumatization is noticeable several years before that age, and comparison of the normal body of the sphenoid bone and that in cases of mongolism reveals that the latter is underdeveloped

The middle cavity appears deep and is overshadowed by the projecting major wings of the sphenoid bone. The posterior cavity shows typical signs The occipital squama is steep and upright, instead of lying in a rather horizontal position behind the foramen magnum. Sometimes the occiput slopes in a way that continues the line of the spine The foramen magnum in several cases was observed to be small and transversely ellipsoid, showing so-called frontal stenosis

A postero-anterior view adds an important fact to the previous observation In a normal skull the supraorbital notch indicates the highest point of the supraorbital margin Laterally, the margin curves downward and articulates at its external end with the frontal process of the zygomatic bone In the mongoloid skull the supraorbital border follows an upward curve toward the external end, forming at this point a rather sharp angle with the zygomatic process Therefore, in cases of mongolism, the supraorbital notch does not represent the highest elevation of the upper orbital margin. As a matter of fact, the slanting eyes of patients with mongolism are caused by slanting orbital openings A study of the upper orbital margin in cases of mongolism indicates the deformity of the skull and is suggestive of the diagnosis of mongolism The Mongolian race does not show such an upward curvature of the orbital margin Lack of formation of the frontal sinus is easily recognizable in the postero-anterior view of the skull of a mongoloid child after the seventh year.

In mongolism the appearance of ossification centers is frequently retarded and as a whole is irregular In the majority of [illegible]

[illegible] (continued) — The distance between [illegible] and nasion is now equal to that [illegible] upper [illegible] n of malar bones The frame [illegible] and the supraorbital [illegible] (at bottom) Diagrammatic tracing of postero-anterior x ray of a 7 month old mongoloid baby Note egg shaped orbit holes, which are slanting upward laterally and preserve the fetal shape The supraorbital foramen is lower than the lateral angle Note the underdevelopment of the malar bones and of the whole maxilla

[illegible] of skull, normal and [illegible] (A, at top) Be-

[illegible]

tween nasal root and crest of upper jaw Note smallness of malar bones (B, middle) Diagram of frontal section through adult skull: note the different shape of orbit holes and the great development of maxilla.

(Legend continued on facing page)

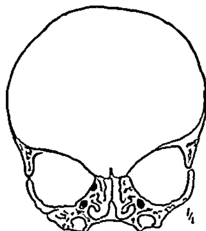
anterior cavity as a whole a curved shape, the floor sloping upward anteriorly and laterally toward the frontal bone. The sphenoid bone is small and the body of the bone underdeveloped. It is noteworthy that neither the frontal nor a sphenoid sinus is to be seen in cases of mongolism Although these sinuses are not fully developed before the seventh year of life, slight pneumatization is noticeable several years before that age, and comparison of the normal body of the sphenoid bone and that in cases of mongolism reveals that the latter is underdeveloped

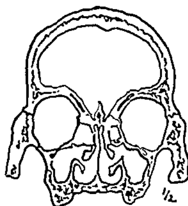
The middle cavity appears deep and is overshadowed by the projecting major wings of the sphenoid bone. The posterior cavity shows typical signs. The occipital squama is steep and upright, instead of lying in a rather horizontal position behind the foramen magnum. Sometimes the occiput slopes in a way that continues the line of the spine. The foramen magnum in several cases was observed to be small and transversely ellipsoid, showing so-called frontal stenosis

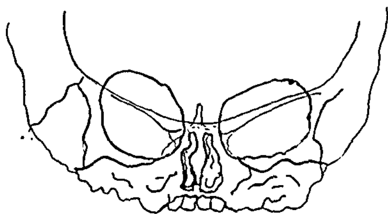
A postero-anterior view adds an important fact to the previous observation. In a normal skull the supraorbital notch indicates the highest point of the supraorbital margin. Laterally, the margin curves downward and articulates at its external end with the frontal process of the zygomatic bone In the mongoloid skull the supraorbital border follows an upward curve toward the external end, forming at this point a rather sharp angle with the zygomatic process. Therefore, in cases of mongolism, the supraorbital notch does not represent the highest elevation of the upper orbital margin. As a matter of fact, the slanting eyes of patients with mongolism are caused by slanting orbital openings A study of the upper orbital margin in cases of mongolism indicates the deformity of the skull and is suggestive of the diagnosis of mongolism The Mongolian race does not show such an upward curvature of the orbital margin. Lack of formation of the frontal sinus is easily recognizable in the postero-anterior view of the skull of a mongoloid child after the seventh year.

In mongolism the appearance of ossification centers is frequently retarded and as a whole is irregular. In the majority of [illegible] capitate [illegible]
In some [illegible]

FIG 26 [illegible]—The distance between [illegible] to that [illegible] upper [illegible] forame[illegible] [illegible] Diagrammatic tracing of postero-anterior x-ray of a 7 month old mongoloid baby. Note egg-shaped orbit holes, which are slanting upward laterally and preserve the fetal shape. The supraorbital foramen is lower than the lateral angle Note the underdevelopment of the malar bones and of the whole maxilla







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After the first three centers have appeared, eruption of new centers is usually delayed until the age of 4 or 5 years, and many a mongoloid has at that point a bone age of 6 to 12 months. After 4 years of age, the appearance of ossification centers is more accelerated. At the age of 15, most mongoloids have a complete set of metacarpal bones, and further growth is arrested.

By x-ray examination the mongoloid hands show some more peculiarities which are not present in cretinism. The bones are delicate, slender and short, and calcification is poor. In a large percentage, the first metacarpal bone of the thumb, which normally has a proximal epiphysis, will show in addition a distal epiphysis. The first metacarpal bone of the index finger, which normally has a distal but not a proximal epiphysis, will show a proximal epiphysis in addition to the distal one. Much more attention has been attached to the middle phalanx of the little finger. This is short and hypoplastic in a large percentage of cases The well known curvature of the little finger is due to the anomaly of the middle phalanx. Hefke has found a curvature of the little finger in 62 per cent, while in my own material I have seen such a curvature in only 36 2 per cent. It is, however, true that, even if the curvature is not outstanding, a slight anomaly is present in almost 90 per cent. X-ray studies of the hand reveal that the index finger also shows shortness of the second phalanx in a considerable number of cases. The end phalanges of all fingers are short and hypoplastic.

With regard to the postnatal growth of the hands, Hefke noticed that the mongoloid hand is from 10 to 30 per cent shorter than is the normal hand I measured the length of the end phalanx and the length of the first phalanx of the fourth finger in 28 x-ray pictures. In this way, it became obvious that the first phalanx is relatively shorter than expected The proportion length of first phalanx to length of third phalanx was below 2 in 7 cases, with an average of 1 61; it was between 2 and 3 in 18 cases, with an average of 2 43 In 2 cases the proportion of 3 was found, and in 1 case the proportion of 4.1 was found In normal x-rays the proportion is 2.5 to 3. We may conclude that those structures which are expected to increase most in size are impaired to the greatest extent, and since the metacarpal bones and the first phalanges have to grow more extensively than the third phalanx, the shortness of those bones is more striking than that of the latter There is, however, an absolute shortening of all three phalanges, and the thinness of the distal phalanx is an important item which does not appear in the measurement of the length.

Although x-ray examination of the hands is sufficient in many cases, it is frequently advisable to include x-ray plates of the pelvis and



FIG 27—X ray of hand of a mongoloid child 3 years of age Most outstanding is the syndactyly, which is, however, not too frequent in mongolism The x ray shows several peculiarities which are frequently found in mongolism Note the distal epiphysis on the first phalanx of the thumb and a proximal epiphysis on the first phalanx of the index finger Note the rudimentary middle phalanx of the little finger and general shortness and delicacy of bones Note the deficiency of calcification Only two metacarpal bones are present, and the epiphysis of the radius is missing Bone age, 6 months

femur These structures offer the advantage that, at the time of birth, the lower end of the femur should show an ossification center, which is expected in the ninth month of intrauterine life The center for the head of the femur should be present at 6 months It is important to confirm the diagnosis of congenital thyroid aplasia by x-rays of the legs, because in this condition the ossification centers will be missing. Retardation of ossification is frequently more marked in the pelvis than in the hands In my material on cretinism the neck of the femur

was found underdeveloped in all cases, and the head was little calcified Dislocation of the hip is not rare. Neck and shafts may form a right angle later in life. The crest of the pelvic bone was irregular and the cartilaginous structure was still present in a cretin of over 15 years of age. A further peculiarity of the long bones of cretins is the presence of rings in the femur and humerus shaft. Wieland has compared these lines with the annual growth rings of trees. Goetzky, Weihe and Wieland describe them as areas of increased density or shadows, while in my material I found the lines which cross the shaft at a certain distance from each other near the distal end brighter than the rest of the bone. The above authors consider these lines as manifestations of "periodic athyrotic inhibition of endochondral ossification" The relationship of these lines to rickets is a matter of argument.

It has been little recognized that in mongolism the ossification of the pelvis and femur shows also greater irregularities than that of the hands. In some cases the picture strikingly resembles that of athyroidism.

These few remarks may suffice to show that x-ray examinations in mongolism are a most helpful aid in diagnosis and treatment and deserve more attention in the textbooks of roentgenology in future editions.

CHAPTER V

MENTAL DEVELOPMENT

INTELLIGENCE

In 1928 Brousseau and Brainerd wrote that "mentally we find that mongol infants show no peculiar defect or perversion that distinguishes them from other aments" The mental development of the mongoloid is, however, as characteristic as the physical development. The statement quoted above shows how little was known about the psychological peculiarities of different groups of the mentally retarded even 30 years ago. Retardation in infants and children of mental levels comparable to the mongoloid is usually the result of brain injury, encephalitis or a developmental disorder of the nervous system The mongoloid child represents the clearest example of deceleration of mentation. The term "unfinished children" is even more appropriate to psychological development than to physical development Shuttleworth, a great expert on mongolism, felt that "the mental condition of defectives of this type is almost as characteristic as the physical"

Speaking statistically, the mental age of an average group of mongoloid patients of all age groups ranges between 2 and 5 years. L Grant Tennies found that the majority of cases remain on a low imbecile level J E Wallace Wallin reported on a large number of cases from St Louis and Ohio, and found that the St. Louis cases varied from Binet age 2 to 7 8 and the Ohio cases from 2.6 to 6.8 M. W. Kuenzel reported on mental ages ranging from 1 to 7. The highest tests were recorded by C Pototzky, who reported mental ages up to 10 8

T[illegible]

tes[illegible]

ch[illegible] mongoloid development are not detectable because tests indicate the limitations in language, vocabulary, counting and solving certain experimental assignments, but they do not take account of inherent potentialities and the capacity to make social adjustments Figure 28 demonstrates the mental development of mon-

was found underdeveloped in all cases, and the head was little calcified Dislocation of the hip is not rare. Neck and shafts may form a right angle later in life. The crest of the pelvic bone was irregular and the cartilaginous structure was still present in a cretin of over 15 years of age. *A further peculiarity of the long bones of cretins is the presence* of rings in the femur and humerus shaft Wieland has compared these lines with the annual growth rings of trees. Goetzky, Weihe and Wieland describe them as areas of increased density or shadows, while in my material I found the lines which cross the shaft at a certain distance from each other near the distal end brighter than the rest of the bone. The above authors consider these lines as manifestations of "periodic athyrotic inhibition of endochondral ossification." The relationship of these lines to rickets is a matter of argument.

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understand why the mongoloid shows special character and psychological traits which are entirely different from those of subjects with other types of mental defect. The mongoloid is not really arrested at any mental level before puberty, but his psychological development is so extremely slow that he is not capable of absorbing more than an infant during childhood and adolescence, and he is still a child when his capacity for mental growth comes to an end.

Striking differences exist between the institutionalized mongoloid and the one who remains with his family in the community. Figure 29 illustrates the findings of a study which was made of 200 unselected mongoloid children (*black dots*) who were seen in the outpatient clinic of the Walter E. Fernald State School. Several aspects of the chart are noteworthy Notice the extremely slow mental development of the mongoloid infant. At an age of one year, not one had reached a mental level of more than six months, and by the age of

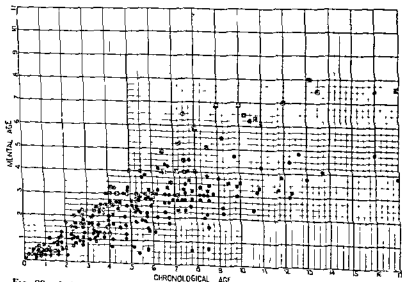


FIG 29—A 10 year study of Stanford Binet mental ages in two groups of patients The *black dots* indicate untreated mongoloid children seen ... patient clinic The ...

... beyond 6 years the

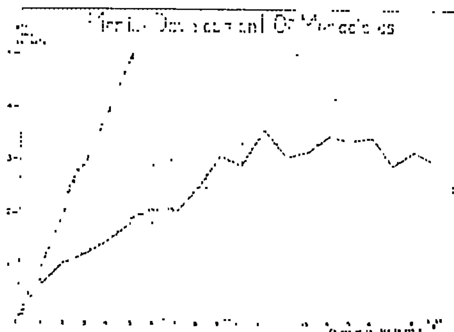


FIG 28 —Mental development in mongolism Punctured line, normal development; unbroken line indicates mental age found in 132 mongoloid patients based on 329 tests.

goloid patients in a state institution on the basis of 329 tests on 132 persons. The diagram shows the mean of different tests on different patients for each age group. The values were corrected to avoid unreasonable ups and downs of the curve due to single tests which were far out of line It may be said, however, that the variations were relatively slight, and no mongoloid in this study was far outside of the average range for the group. The average mental age ranged from 2½ to 3½ years. This study, however, is not representative of all *mongoloids and does not consider their "social maturity." Children* of this type develop much better if they have individual care and attention at home or in private schools in which they live in small groups. In large institutions, in which the mongoloid is placed with other types of mental defectives, no emphasis can be put on his special needs, and the majority remain on a lower level of achievement than can be attained with special attention. The chart, however, reveals one startling aspect: It shows that between 1 year and 10 years of age the mongoloid child passes through mental levels of from 1 to 3 years. The mongoloid is an infant for the first 10 years of his life; in other words, it takes him 10 years to accomplish what the normal child accomplishes in three years. With this approach, one can easily

on observations made in the community outside of institutions. It is of the greatest importance that medical treatment and educational training be continued over a long period

EMOTIONAL RESPONSE

Mongoloid children, if treated well, are often lovable little beings, full of affection and tenderness. A visitor at an institution summarized her observations as follows "As playmates, they are always hugging and kissing one another with vague but genuine smiles of affection. They come up and put their arms round the stranger as confidently as a puppy jumping up on a visitor, and though not understanding a word said to them, good naturedly answer yes to any question, hoping that will please"

MIMICRY

An astounding gift of mimicry has been considered one of the most conspicuous psychological traits of mongoloids, and yet everyone familiar with child psychology knows that mimicry is the outstanding characteristic of a normal child between 2 and 4 Time and again parents are delighted and proud to see their infant child observe certai[illegible]
cil [illegible]
a y [illegible] faculty of mimicry is a most important psychological asset in early childhood, and no normal infant would learn to talk or eat and behave without an inborn aptitude for mimicry The faculty of mimicry in the mongoloid is, therefore, not a character trait of this condition, but a manifestation of his protracted infancy. For each developmental step, the mongoloid needs so much more time than the normal child that one may say he represents a slow motion picture of human development Since, in the majority of cases, the film is broken either by premature death or by arrest of mental growth, the mental capacities are never fully utilized

STUBBORNNESS

A word should be said about a very characteristic behavior pattern of mongoloid patients· their stubbornness Although the meaning of the word is familiar to everybody, the underlying behavior has not attracted sufficient attention as an elementary psychological trend A stubborn person is defined as "inflexible in opinion or intention, unreasonably obstinate, characterized by perseverance or persistence." The psychiatric term "perseveration" has, however, a slightly different meaning It indicates a persistence of associations, thoughts and

two, only a few had achieved the mental development of a normal one year old. After the age of two, the mental growth proceeds at a fairly uniform pace until the age of six, when the curve seems to level off. In this study, only one child reached a mental level of more than five years. The mental ages of the eight year olds, for instance, ranged from as low as six months to as high as four years six months. The untreated children were compared with a group under treatment (*circles*). The significance of these observations will be discussed in chapter XI.

The potential mental development depends on the degree of biologic maturity present at birth and the amount of training and therapy given during infancy and childhood.

It is interesting to note that those writers, like Pototzky and A. M. Gordon, who have published data on higher mental ages in mongolism, have dealt with mongoloid adults. In Pototzky's material, the highest mental age of patients below 10 years of age was 5 years and 7 months. The patient with the highest rating had received training for the previous two years All patients with a mental age above 7 years were chronologically above 18 years of age. We usually do not utilize the mental plasticity of mongoloids in the second decade of life. Training is stopped too early. Pototzky has also observed that the "social maturity" of mongoloids is above their mental age. This statement confirms the observation which I reported above, that mental age does not accurately suggest the personality patterns of mongoloid children. Their emotional interaction with other persons enables these children to participate in the activities of their surroundings

The mongoloid's difficulty with abstract thought is seen in his inability to count and to understand the meaning of numbers Many mongoloid children of 6 to 9, even those with a fairly good vocabulary, have great difficulties in counting and using numbers Arithmetic concepts on a first to third grade level are impossible for the mongoloid child. However, not too much attention has been given to the development of number concepts in these children, and earlier systematic training may be helpful.

The low opinion of the potentialities of mongoloid persons is based on observations in large institutions or on single cases which have had little attention Reports and observations on those mongoloids who remain in the community or are pupils of smaller institutions show that the number of mongoloid children who maintain an IQ of 60 to 70 when growing up is not as small as one would expect from earlier publications. This statement is based on personal communications from psychologists and parents from all over the country and

on observations made in the community outside of institutions It is of the greatest importance that medical treatment and educational training be continued over a long period

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words from which the patient is unable to depart. As a behavior pattern, stubbornness is the inflexibity of intentions. Stubbornness can be observed in very young mongoloids and seems to depend upon their inability to shift quickly from one object to another and to react to new situations With great patience, the stubbornness may be overcome in a certain test condition, but it remains a fundamental tendency of the patient in all new situations. Contrasted with the lack of attention and the distractibility common to many subnormal patients, I venture to suggest that the stubbornness of mongoloids is a psychological manifestation of the peculiar discrepancy in the development of the nervous system, in which the central subcortical areas serving emotional responses are fairly well developed, while the "long-circuiting" system of the cortex, serving the evaluation of sensory stimuli and responses, and therefore, intelligent interaction with the environment, remains immature and underdeveloped.

MOTOR DEVELOPMENT

The development of motor abilities in the child with mongolism is very slow during the first year. In the first three months, spontaneous movements and kicking may be of a normal nature, but the mongoloid baby is usually very quiet and sleeps most of the time. Even at feeding times, it is not restless and will seldom indicate its wants by vigorous crying. In this respect, many mothers remark that the mongoloid was "the best baby we ever had. It never made any trouble." The retardation manifests itself more in this general lack of attention and responsiveness than in conspicuous shortcomings. When awake and exposed to adverse conditions, the mongoloid who *appeared weak and apathetic a moment before may suddenly display* great strength and resistance. We frequently encountered surprising resistance in babies of four to six months when attempting to take x-rays; sometimes three people were needed to control such a small baby It is not lack of strength or muscular power at this age that makes these children lax and limp, but the immaturity of the nervous system, which apparently requires powerful stimuli to reach the threshold level.

At an age when the normal child sits up and keeps his body erect, the *mongoloid child will not even make the attempt* In the second half of the first year, the motor retardation becomes more conspicuous with every passing month. Rarely does a mongoloid child sit up before the end of the first year, and he usually will not try to crawl until long after the first year has passed As pointed out before, each step in the development is extended over a long period.Years may elapse

between the time that the child learns to sit up and the time that he learns to stand. A similar time lapse may occur between learning to stand and learning to walk. Even normal children vary to some degree in the time at which they can walk independently. In general, the average child will begin to walk between 11 and 16 months. Roughly speaking, the mongoloid child rarely attempts to walk before the beginning of the second year, and the majority do not start before they are three years old. It is not unusual for the first steps to be postponed until the age of four, five or even six years. It may be said, however, that *every mongoloid child can learn to walk*, except if a handicap like club feet or some prohibitive neurologic condition is present

A child's potential ability to walk can be fairly accurately estimated by the time he is one year old. At that time the amount of hypotonia and the measure of his inability to balance in an upright position can be determined If the child is able to stand up and shows a strong tendency to sustain himself in an upright position, he can be expected to walk between 20 to 24 months of age If he is hardly able to sit up at all, or is unable to maintain a sitting position for an indefinite length of time, one can predict that the child will probably not walk before he is three years old

The acquisition of perfect motor control after a child has started to walk takes from one to two years for normal children At the age of two, most infants can walk on a broad base, but even at three years of age, motor control is not perfect As must be expected because of characteristically slow development, these patterns extend over a longer period in the mongoloid than in the normal child. His gait is conspicuously infantile until he is about 6 years old, and many mongoloid children always walk on a broad base Arm movements are clumsy and awkward Great accuracy of motor control is rarely achieved, and even those with high mental ages have imperfect motor control

SPEECH

Human ...
the
of ...

... manner, addressing their "Ma" and their "Pa" in one syllable. They may also employ single syllables to refer to objects The use of single words to express wishes comes much later, and the use of sentences is actually evidence of employing lan-

words from which the patient is unable to depart. As a behavior pattern, stubbornness is the inflexibity of intentions. Stubbornness can be observed in very young mongoloids and seems to depend upon their inability to shift quickly from one object to another and to react to new situations. With great patience, the stubbornness may be overcome in a certain test condition, but it remains a fundamental tendency of the patient in all new situations. Contrasted with the lack of attention and the distractibility common to many subnormal patients, I venture to suggest that the stubbornness of mongoloids is a psychological manifestation of the peculiar discrepancy in the development of the nervous system, in which the central subcortical areas serving emotional responses are fairly well developed, while the "long-circuiting" system of the cortex, serving the evaluation of sensory stimuli and responses, and therefore, intelligent interaction with the environment, remains immature and underdeveloped.

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prevent the child from understanding the meaning of what is taught. If they are ready for them, mongoloids may improve greatly through exercises designed both to strengthen the muscles of the jaws, lips and

exercises, is useful in improving the motor aspects of talking, and instruction both in vocabulary and the meaning of words is advised when the proper mental level is reached

Some attention [illegible]

10 or more years ago than today This seems to be due to the great general improvement of nutrition in institutions as well as in the community. In cases of thyroid deficiency and myxedema, the voice becomes raucous within a short time but usually returns to normal after thyroid treatment It is suggested that the gutteral voice in mongolism is due to myxedema and swelling of the mucous membranes, which are often dry and thickened The harsh voice is rarely found in patients who have been treated with thyroid over a long period.

SENSORY DEVELOPMENT

It goes without saying that sensory examination meets with great difficulties on account of mental retardation, but most textbooks seem to take it for granted that the sensory examination is negative. This does not seem to be borne out by clinical observations and the pathology of the nervous system Moreover, sensory acuity is partly a motor phenomenon, and clumsiness and high sensory accuracy rarely go hand in hand

The vision seems impaired by strabismus The lack of myelination of the optic nerves does not suggest very accurate perception Moreover, many mongoloids are short sighted and astigmatic The sense of smell is poor, owing to several factors, one of which may be of a central nature and another due to the chronic rhinitis with alterations of the mucous membrane It is impossible to judge the accuracy of hearing Although true deafness seems to be rare, nothing suggests very accurate hearing discrimination.

A notion exists

guage as a means of communication. Because speech is a complex development, different investigators mark its beginning at different places.

Several studies have been made that aid in estimating the amount and rate of speech development that can be expected from children with mongolism. According to Millicent Strazzulla, moderately retarded mongoloid children with IQ ratings between 40 to 70 begin using words at an average age of 33.4 months, using phrases at 48 months, and using sentences at 60.8 months. Some children in a more severely retarded group were slower in speech development, but approximately half of them used sentences at an age of about six years

Gesell and Amatruda estimate that the child with mongolism uses "*words and possibly phrases at 3 years . . . [and] speaks sentences at* 6 years." Institutionalized children start to talk much later In a study by Engler, he found that by the age of three years, only 49.4 per cent of the children had begun to speak, 61.7 per cent by the age of four years, and 81 2 per cent by the age of five years. After five years, therefore, 18.8 per cent of mongoloid children were still incapable of speech An earlier study made by Durling and this author showed *that among the institutionalized mongoloids of 16 years of age and* older, 47 per cent of the cases had mental ages of less than two years 11 months and were not using words.

Speech development usually lags one to two years behind walking, and in general, a child cannot be expected to use language before walking has been established Only in those cases in which an extreme degree of hypotonia (double-jointedness) is present may speech development *actually precede walking.*

There are certain characteristics in speech patterns Many mongoloids have difficulty pronouncing certain letters, and many speak so indistinctly that only their near relatives are able to understand them. Stammering is not rare in very anxious children, particularly among the more intelligent ones who feel that they are under too much pressure. Although the vocabulary is often limited, in certain cases an *amazingly large vocabulary may be observed. Comprehension* is usually superior to expressive language. There is a general inability to abstract. Many children with mongolism have a very good memory, and although it may take a longer time to acquire new words, they are retained quite well. Some children have an almost photographic visual memory for situations. Learning will advance more rapidly in a play situation than if the child is put to a test. In all speech training, *the physiologic* aspects of hypotonia, ataxia and anomalies of articulation have to be distinguished from the mental disability which may

Clinical observations suggest that touch and pain as well as heat and cold discrimination are poor. The children feel little pain when operated on for minor boils and sores. They are likely to acquire many skin disorders without calling attention to them, while other children of the same mental level would show discomfort.

With these facts in mind, one may ask to what purpose a mongoloid child may best be trained The highest mental age of children below 10 is usually around 5 years. Under the most favorable con- [illegible]

tal development can be expected in the period from 10 to 20 years, and education should not stop too early

Mongoloid children should not be trained with other low grade mentally deficient children unless necessary, because most of the retardates of other types are not capable of much progress, whereas the mongoloid has dormant possibilities of improvement. He benefits most from a kindly atmosphere and should be surrounded by children of higher intelligence, because he learns best by copying other people.

Most mongoloids are unable to help in any trade requiring skilled motor control. They are rarely capable of doing industrial work, sewing or carpentry This limits their usefulness, even when the mental age would permit employment in such lines of occupation The mongoloid girl is best used in housework, and may learn to do routine work in a routine manner. She may lead a quiet life around the house, because these children learn to stay at home, do little errands, respect traffic rules and keep out of mischief Mongoloid boys will be best engaged in garden or farm activities, if not too great an accuracy is required

INSTITUTIONALIZATION OR HOME CARE

Observations on the mental development of children with mongolism indicate that even such a relatively uniform [illegible]

One difficult problem concerns the conditions under which institutionalization is desirable. For many years pediatricians have expressed the opinion that the [illegible] ld be institution- [illegible] should not even [illegible] onal bond which

goloid's "idea of time" as "remarkable" Brushfield ..., in observing a group of 177 mongoloids, noted that all of them could hum a tune "correct in note and time."*

Although it is not possible to prove a special rhythmic sense in mongoloid children, the faculties of mimicry and rhythmic expression may both be due to the fact that children with mongolism retain certain inf[illegible] ual, which serve useful purposes [illegible] Between the ages of six months [illegible] an inclination to mimicry and a clear response to rhythm, using these features to assimilate needed abilities from their surroundings. The child with mongolism not only passes through this developmental stage at a slower rate but retains some of its vestiges throughout life, since his retarded powers of abstract thought make for less interference with expressional behavior than there is in the child of normal intelligence.

Very few studies have been made on sensory discrimination in the mongoloid because of the difficulties pointed out above. One promising effort has been made by A M Gordon. He studied visual and tactile discrimination and compared the results with those found in normal children of the same mental age. The studies were made on mongoloid adults whose mental ages ranged from 5 years 3 months to 6 years 8 months The mongoloid patients proved to be inferior in tactile discrimination to the group of normal children equated with them for mental age It is interesting to note that all mongoloid patients, with one exception, tested higher on visual discrimination than on tactile tests, while the normal controls tested higher on tactile discrimination than on visual tests, with two exceptions. It may, however, be said that all mongoloids tested lower than the normal controls on the visual tests in spite of having the same "mental age" In addition to the Stanford-Binet form L, the Arthur performance test and the Vineland social maturity and educational achievement tests were used. All tests showed a high intercorrelation, and those mongoloids who ranked first in one test were likely to rank high in other competitions too. Only slight changes in rank place were observed There was, however, no correlation between any of these tests and tactile discrimination. The patient with the lowest mental age scored the highest tactile discrimination, and the poorest performance was seen in a patient with a mental age of 5 years 10 months. The conclusion to be drawn from this study is that mongoloids are poor in tactile and fine motor discrimination, both of which are probably aspects of the same somesthetic system.

* Cantor, G. N , and Girardeau, F L · Rhythmic discrimination ability in mongoloid and normal children Am J Ment Deficiency 63 621, 1959

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INSTITUTIONALIZATION OR HOME CARE

Observations on the mental development of

One difficult problem concerns the conditions under which institutionalization is desirable. For many years pediatricians have expressed the opinion that the mongoloid child should be institutionalized immediately after birth, and that the mother should not even see her newborn child, to avoid creating an emotional bond which

would make it difficult to separate them later if necessary. Experience, however, has shown that this opinion cannot withstand psychiatric criticism. Great emotional distress has been observed in mothers who, having given up their babies immediately after birth, visited their infant children at a later age. They were often surprised to see how nice-looking and responsive the infants appeared, and they felt guilty for having given up the children at too early an age. Since most mongoloid babies do not look very different from the average newborn, seeing the child is not a real shock to the mother. She can gradually become accustomed to the idea that the child may have a slower development than the average. It can be explained to the siblings and relatives that the child has a more or less severe congenital heart defect, and because of a circulatory insufficiency, the mental and physical development of the child may be slow and hospitalization necessary at a later date.

As to the development of the mongoloid infant, it goes without saying that the child develops much better in the home than in even the best institution In 1956 Malcolm J. Farrell pointed out the adverse effects of early institutionalization on mentally subnormal children. He reiterated the many observations which have been collected with regard to the ill effects of too early and too long hospitalization, effects which are now generally known under the term of "hospitalism"

The early years of the mongoloid infant are not different from those of any other baby except that the steps in development take place somewhat later than normally The child will be unable to sit up by himself before he is 9 months old, and maintaining equilibrium, standing up, walking and talking will be delayed. However, the child will respond to affection and attention like any other baby, and his behavior will depend greatly on the way in which he is handled Anxiety and tension are easily transmitted to the infant and produce signs of restlessness and frustration Feeding difficulties, common in mongoloid infants because of the immaturity of the digestive tract, may be exaggerated and persist, due to psychological factors

Whether a child with mongolism should be institutionalized and when should be decided after a careful consideration of the whole family situation.

If [illegible] latecomer, there is no urge [illegible] alth of the parents requires [illegible] to be institutionalized when there are no training opportunities in the community and when the child has no one of his own age to play with. It is not too good if

he lives alone with his parents, though they be loving and devoted, for they may spoil him and unintentionally delay his maturation. The child with mongolism needs contact with other children who are more intelligent and from whom he can learn adequate behavior. Many good-looking mongoloid children are able to attend normal nursery classes when they are 3 and 4 years old. Such a child does very well if he is the only mongoloid among a group of normal children. Parents may be advised not to use the term "mongolism," and speak only of slow development, since the term "mongolism" creates prejudice in teachers and in parents of other children, and prevents the acceptance of the mongoloid child.

Mongoloid children of school age will have to attend special classes according to their IQ levels There are quite a number of children in the educable group (IQ's over 50) who therefore are entitled to go into regular special classes created for these children The children whose IQ's are far below 50 profit from attending sub-special or opportunity classes since the socialization of the mongoloid child is an important part of his education.

Since mongoloid children are often very confused in new and strange settings, many educable children who have an IQ of over 50 will score low ratings in a new and unexpected setting. Many school psychologists and school superintendents exclude these children from classes for the educable on account of such a single test performed under adverse conditions It must be emphasized that the child should not be judged from one test performance

Many mongoloid children, ages 6 to 12, have a difficult time because of restlessness, destructiveness, and a lack of understanding what is expected of them These children pose very severe problems to the parents, especially to mothers Some devoted mothers spend all their time in the supervision of the mongoloid child, considering it their duty to give all their attention to this unfortunate being. They may neglect the other siblings with the idea that they are fortunate and normal, and therefore do not need mother's attention This creates a very unhealthy family setting, and the attending physician should use all his influence to help the parents to come to a reasonable solution of their problems. Many mongoloid children of school age are actually much happier in boarding schools where they are among their equals Moreover, boarding schools provide not only scholastic education but adequate recreation and entertainment. They usually have better workshop facilities.

If the mongoloid child is in the middle of a number of siblings or even the oldest child, the upbringing of the younger children poses

would make it difficult to separate them later if necessary. Experience, however, has shown that this opinion cannot withstand psychiatric criticism. Great emotional distress has been observed in mothers who, having given up their babies immediately after birth, visited their infant children at a later age. They were often surprised to see how nice-looking and responsive the infants appeared, and they felt guilty for having given up the children at too early an age. Since most mongoloid babies do not look very different from the average newborn, seeing the child is not a real shock to the mother. She can gradually become accustomed to the idea that the child may have a slower development than the average. It can be explained to the siblings and relatives that the child has a more or less severe congenital heart defect, and because of a circulatory insufficiency, the mental and physical development of the child may be slow and hospitalization necessary at a later date.

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Whether a child with mongolism should be institutionalized and when should be decided after a careful consideration of the whole family situation.

If the mongoloid is the youngest child and a latecomer, there is no urgency for institutionalization unless the health of the parents requires such a step. These children may have to be institutionalized when there are no training opportunities in the community and when the child has no one of his own age to play with. It is not too good if

physician and the parents should realize that no binding decisions can be made until all aspects of the case are clearly understood. Whether a child should be institutionalized or stay at home is a question which has to be re-examined every year. Especially in the case of a young child, the physician should evaluate the situation together with the parents, and see what must be done at that specific moment and what should be done within a year. Often parents have quite different ideas as to what should be done. Family conflicts precipitate around a subnormal child, and the emotional reactions of all the relatives involved have to be carefully studied in order to come to satisfactory compromises The physician who treats the mongoloid child faces a family and not a single person. Those physicians will be most helpful whose decisions are made after a careful evaluation of the total situation

severe difficulties. Not only may the care of a new baby or a number of smaller children require the full attention of the mother, but younger children naturally look up to the older sibling and take him as an example for their own behavior. In the interest of the younger children and the whole family climate, early institutionalization is often *indicated for a first-born mongoloid or the one in the middle* of the birth order.

The special education necessary for the child with mongolism is well established, and it is not necessary to discuss his specific needs here. It is obvious that the child with mongolism should be educated not according to his chronologic age but according to his mental age and capacities. The children vary greatly in their abilities. Some develop a large vocabulary and may be good spellers, but have poor number concepts. Other children do quite well with numbers but other abstract concepts remain a problem.

It is obvious that practical sense requires careful training to enable them to fulfill some practical tasks as adolescents and adults. Unfortunately, too much attention is paid to scholastic training or other impractical activities, like typewriting, for which they will have little aptitude later. Thus, working activities *should* complement the scholastic education from the early 'teens on.

It has been emphasized that most mongoloid children have a rather placid and agreeable constitution and respond well to affection and a generally peaceful climate. It must be said, however, that this is not true of all mongoloid children. Some very devoted parents are deeply disturbed by the destructiveness, aggressiveness and lack of manageability of their mongoloid *child* and feel guilty about it. Such behavior is often the result of organic processes in the brain; some mongoloid children need tranquilizers if they are to stay in the family Other problems arise from the discrepancy between inadequate judgment and unusual strength. This necessitates control of their activities which often deprives these children of acting out their normal needs. The child with mongolism loves to be with his mother or in the company of others, and *he* enjoys playing *in the kitchen, living room* or wherever the family gathers. It is quite important to teach the mongoloid child to play at least for certain hours of the day in a playroom, even alone, and to provide room for his activities wherever this is possible.

In summarizing the psychological observations and needs of the child, one may say that the rearing of children with mongolism requires individu*alization in each case according to the de*mands of the total situation. It also requires periodic readjustment. The attending

sections, the anomalies of the brain are another instance of the "molecular" disorder which characterizes the growth and differentiation of the mongoloid child in the prenatal period. The anomalies of the nervous system are a manifestation of the fundamental organogenetic disturbance which interferes with the normal development of the unborn child and results in "mongolism."

In spite of the frequency of mongolism and the large material which has been available for research in recent decades, there is almost a complete lack of reliable studies of the central nervous system. Even the book *Mental Subnormality* by Masland, Sarason and Gladwin, published in 1958, quotes two neuropathologists of experience (N Malamud and O T. Bailey) as stating that the changes observed in mongolism are "relatively nonspecific" and "remarkably minor in degree"—a position which is quite contrary to my own observations. These statements, and others of a similar nature, can be explained only by the fact that the investigators had not conducted a thorough study of the central nervous system in mongolism. Such a developmental disorder needs a specific approach in which due recognition is given to the problem of the time factor in development and de-

... important factor in the pathology, the "heterochrony." "Heterochrony is an irregularity in time relationships: specifically, in evolution, a deviation from the typical sequence in time in the formation of organs or parts"

It is therefore unnecessary to go into detail with regard to earlier literature except for those investigations which have added significant observations to the understanding of the neuropathology of mongolism Roessle (1923) introduced the term "dyscerebral dwarfism" to distinguish those cases in which the physical growth disorder depends on the pathology of the brain from the ones in which a primary deficiency of the endocrine glands is present. Roessle was well aware of the severe dyscerebration present in this condition Van der Scheer's collaborator, Gans, published several studies about the microscopic anatomy of the brain and called attention ... developmental

... iber flocculus"

... The pons and

... very small, weighing in each case about half an ounce, whereas the usual weight is nearly twice as much. The cerebral vessels are inclined to be much thinner than in healthy brains"

Bourneville (1902) mentioned the smallness of cortex and white

CHAPTER VI

ANOMALIES OF THE NERVOUS SYSTEM

Observations indicate that the retarded mental development (often rather severe) in children with mongolism depends on anomalies of brain function and brain structure. We have demonstrated in numerous investigations that the physical growth disorder represents a very complex disorder in which the central growth regulation is at fault. The endocrine system functions abnormally, and the growth patterns of the mongoloid deficiency follow patterns of a congenital acromicria. But a pituitary disorder is not the "cause" of mongolism. As I pointed out in the first edition of my book *Mongolism and Cretinism,*

> Pituitary function on its part depends on the brain, which receives the stimuli from the outside world and primes the organism as a whole for proper responses. Extensive studies of the nervous system reveal that the nervous system is immature at birth and develops at a much slower rate than necessary. The vicious circle between brain and endocrine system keeps the mongoloid child out of tune with normal development and, if left to its own resources, the mongoloid child falls consistently further back in its mental and physical growth.

Although the mental defect varies in degree from IQ levels below 25 to intelligence levels near the borderline, the proposition that mongolism can be associated with perfectly normal intelligence is impossible by definition. Normal children may have some of the physical aspects seen in mongolism in the form of infantilism, underdevelopment of the sex organs and a variety of endocrine dysfunctions—none of which is specific within the mongoloid congenital acromicria—but such findings do not justify a diagnosis of mongolism in an otherwise normal child. The term mongolism has been coined for a specific form of mental deficiency, associated with certain physical characteristics, and should be reserved (if maintained) for this specific morbid entity.

In pointing out that the physical growth deficiency in postnatal life must depend to a large extent on abnormal functioning of the brain, we do not state that the mongoloid characteristics are depend-

sections, the anomalies of the brain are another instance of the "molecular" disorder which characterizes the growth and differentiation of the mongoloid child in the prenatal period. The anomalies of the nervous system are a manifestation of the fundamental organogenetic disturbance which interferes with the normal development of the unborn child and results in "mongolism."

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Bourneville (1902) mentioned the smallness of cortex and white

matter. The smallness of the white cores was also noted by Hellemann, who observed retarded myelination, a diminished amount of white matter and lack of cytoplasm in the nerve cells.

Sergio Levi (1936) found the brain weights less than those of normal individuals of the same age and sex. "The relative development of the frontal lobes was less than normal. The cerebral cortex showed a diminished development and differentiation from normal."

Leo M. Davidoff (1928) summarized his observations as follows:

I have found few morphologic changes which are constant, with the exception of a small cerebellum and brain stem, the embryonic convolutional pattern, and my own observation of the small content of the ganglion cells of the third cortical layer. The process by which the latter defect arises cannot be determined with certainty from the appearance of the preparations

L. O. Morgan studied alterations in the hypothalamus in mental deficiency and included observations on six mongoloid brains. He succeeded in making exact cell counts and found a normal appearance of the hypothalamic nuclei proper, but found reduction in the number of cells in the nucleus supraopticus. The reduction ranged from 13 to 60 per cent, the tuber lateralis was affected to a greater degree, ranging from 29 to 74 per cent, and the substantia grisea was less affected

In order to understand the neuropathology of mongolism, one has to start with the clinical observations. The newborn mongoloid is extremely hypotonic; during the first few months he usually lies in his crib, rather lifeless and apathetic and without mental responses. Although the child may kick and move to a certain degree, the motions are not coordinated or a part of motor expressive behavior Even strong mongoloids seem unable to sit up, keep their equilibrium or stand at the usual time, and they do not start to walk until they are almost 2 years old.

A neuropathologic study must therefore deal with the following questions: In what way is the brain of the mongoloid newborn and infant different from the normal? Are there indications of arrested development at a certain stage in the prenatal development, resulting in brain malformations? Is the brain maturation different from that of the average newborn and infant? Is the nervous system maturing at a slower rate than normal? To answer these questions, there must be a comparative study of normal brain development and that of the mongoloid brain. Step by step, we must find out whether the maturation of the mongoloid brain differs from the normal. Mongolism being present at birth, the findings in the infant and young child will be of special significance since the alterations found in this age group

must be of rather recent date In older children and adults, there are many degenerative and secondary changes which are likely to confuse the picture and often make it impossible to discriminate between primary and secondary pathology. Studies of the spinal cord and brain give indications of a prenatal developmental disorder dating to the first trimester of fetal development. Over 80 brains and about 50 spinal cords were available for this research. The patients ranged in age from two days to 60 years The neuropathology of mongolism is quite uniform and characteristic, despite the variations in degree of alterations.

Although in general the weight of the brain is characteristic only to a certain degree, the low brain weight of mongoloid infants cannot be considered a result of degenerative changes as found under normal conditions in old people The weight of the brain in the mongoloid child is considerably less than that of a normal child of the same chronologic age A low brain weight, together with other observations, suggests that the brain has not reached its full maturation and should be considered "immature"

THE BRAIN

The [illegible]
to [illegible]
bra[illegible] grams In the first year the brain weight rises to 650 grams, and in the second year to 900 grams By 2½ years, the average weight is about 1100 grams, and after 3½ years it exceeds 1200 grams Table 5 shows the great retardation in brain weight over the first 8 years By the end of that time, only three brains had reached a weight greater than 1000 grams, which corresponds to the brain weight of a normal child of less than 2½ years of age. Though the table indicates that brain development is very much retarded, it shows that some development does take place, although it never reaches the level of a normal person.

In the first case (table 5) with a given [illegible]
[illegible] fetal month, but a [illegible] Cm ; the liver weighed 44 Gm , the spleen weighed 4 Gm , and the kidney 10 Gm —all measurements which indicate that the child was about 2 months premature In correlation with the other organ weights, the brain was normal for the eighth fetal month The next five brain weights appear also premature from a physiologic point of view.

The brain of the mongoloid baby is essentially immature. The con-

TABLE 5.—*Weight of the Brain in Mongolism*

No.	Age	Sex	Body length (cm.)	Weight of brain (Gm.)
1	2 days	F	40	218
2	6 weeks	F	49.5	432
3	1 month, 19 days	M	48.2	465
4	2½ months (2 mo. prem.)	M	47	388
5	3 months (1 mo. prem.)	M	52	409
6	2 months	M	—	315
7	3 months	F	—	500
8	4 months, 3 days	M	53.3	440
9	4 months, 15 days	M	53.3	545
10	5 months	—	—	352
11	5 months	M	56.5	650
12	5 months	M	58.3	610
13	5 months, 11 days	F	58	660
14	6 months	M	—	760
15	6 months	F	60	770
16	7 months	F	65	650
17	7 months (3 wks. prem.)	M	58.5	550
18	8 months	M	63	790
19	9 months, 7 days	F	61	575
20	10 months, 8 days	M	63.5	715
21	11 months	F	—	650
22	12 months	F	—	836
23	12 months	F	—	730
24	13 months	M	70	722
25	18 months	F	72	678
26	18 months	M	—	940
27	18 months	F	—	725
28	21 months	F	—	820
29	21 months	M	—	850
30	23 months	M	—	880
31	23 months	M	—	1,050
32	2½ years	M	—	750
33	2½ years	F	—	983
34	2 years, 8 months	F	75	830
35	4 years	M	—	920
36	4 years	F	96.5	940
37	4 years, 7 months	F	78.7	740
38	5 years, 3 months	M	88	970
39	5½ years	M		1,045
40	6 years	F		875
41	6 years	—		855
42	7 years	M		845
43	7 years	M		1,065
44	8 years	M		800
45	8 years, 5 months	—		1,290
46	8 years, 7 months	F		1,120

TABLE 5—*Continued*

No	Age	Sex	Body length (cm)	Weight of brain (Gm)
47	9 years, 5 months	M	114.3	1,185
48	9 years, 8 months	F		1,044
49	10 years	M		1,225
50	10 years	M		1,295
51	10 years	F		1,025
52	11 years	M		1,124
53	12 years	F		1,110
54	12 years	F		990
55	13 years	—		1,105
56	13 years	M		1,070
57	14 years	M		1,220
58	14 years, 5 months	M		1,100
59	14 years, 7 months	M		1,180
60	15 years	F		1,184
61	15 years	M		1,290
62	16 years	F		980
63	16 years	—		985
64	17 years	M		1,140
65	18 years	—		1,058
66	18 years	F		1,160
67	20 years (2 mo prem.)	F	124.5	960
68	20 years, 5 months	M		1,295
69	22 years	—		1,248
70	22 years, 7 months	M	145	1,125
71	23 years	M		910
72	24 years	—		1,034
73	24 years	M		1,275
74	25 years, 6 months	M	143.5	1,060
75	26 years	—		1,120
76	26 years, 7 months	F	139.7	1,300
77	30 years	—		1,260
78	33 years	F	101.6	1,200
79	33 years, 2 months	M		1,370
80	37 years	M		1,080

volutions are small and not broad like those seen in older cases. Myelination is not up to date, and the brain appears softer and of a different color from normal. It is frequently yellowish and wax-like. Most outstanding is the smallness of the cerebellum, whose retardation seems more pronounced than that of the cerebrum.

Concerning the shape of the brain, figure 30*A* shows the brain of a mongoloid infant 22 months of age. The original fissural and convolutional patterns are not abnormal, but there is flattening of the convolutions and compression of the frontal and temporal poles All brains

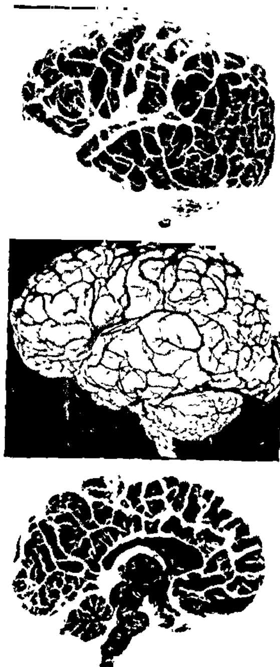


FIG 30—(*A, at top*) Lateral view of brain of 1 year 10 month old mongoloid baby (42/102) *Note distortion of fissures of lower temporal lobe, accordion-like coronal fissuration with deviation of all fissures* that normally run in a sagittal direction; underdevel*opment of frontal poles with* retroflexion; hypoplasia of cerebellum. (*B, middle*) Lateral *view of brain of 4 year 5 month* old mongoloid girl (40/57) Note hypoplasia of frontal *poles with retroflexion, com*pression of temporal poles with deviation of fissures, compres*sion of occipital poles, hypo*plasia of cerebellum Some of the temporal convolutions are *flattened* (*C, at bottom*) Medial aspect of the brain seen in (*A*) Note short corpus callo*sum and hypoplasia of brain* stem and medulla, marked hypoplasia of cerebellum, which *lies partly in the foramen mag*num

of that age group show a more or less pear-shaped outline, viewed from above. The base of the brain shows some noteworthy peculiarities. The gyri recti are flattened, having been pressed against the cribriform plate, whereas the lateral parts of the inferior frontal lobes are compressed and slant upwards *from the steeply arched orbit roofs;* the frontal poles are markedly flattened; the temporal lobes are dis-

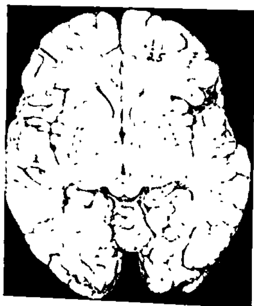


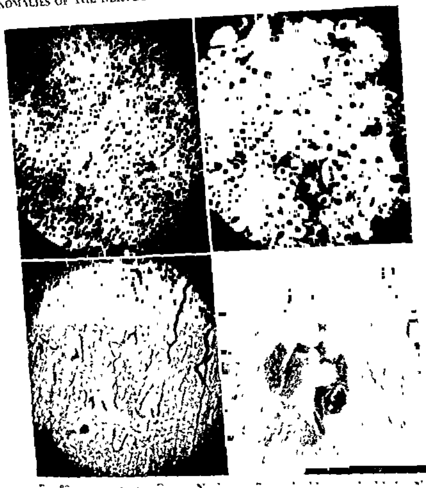


FIG. 31 — ... 2 ... and ... ma ... ar ... ter, ... primitive brain with "simple patterns." Note smallness and asymmetry of frontal lobes. Convolutions broad. Gray matter wider than normal; irregular outline

torted and twisted. The cerebellum is pushed forward, and the brain stem originates almost anteriorly from the center of the brain (fig. 30*C*). In the lateral view the upward push of the frontal poles is striking. The brain convolutions anteriorly from the vertical branch of the sylvian fissure are compressed. There is also striking distortion of the temporal lobes. The superior and medial temporal fissures are pushed upward. The anterior pole of the temporal lobe is twisted and the superior temporal gyrus compressed.

On horizontal sections the impact of the operculum into the sylvian fissure is conspicuous. The insula is compressed and the anterior part of the sylvian fissure partly fused. The frontal poles appear markedly fused and markedly compressed. It is worth mentioning that at that age the ventricular system is not yet compressed. The pia arachnoid is more adherent than normal, and the stripping off produces decortication of the convolutions because of adhesion of the pia to the first cortical layer. Microscopic examination reveals that the first layer is thinned out and the margin of the convolutions roughened. In the frontal, temporal and occipital lobes many convolutions are tightly pressed against each other, and there are many points at which the roughened walls of the fissures form glia bridges which close the fissures either partly or completely. The phenomenon of beginning fusion is recognizable on many slides. The tips of many convolutions are tilted and the surface is flattened

A microscopic study of the cellular and myelin structures is of great interest The nerve cells of the cortical layers are dense, but the tissue appears mottled, and stripes devoid of nerve cells run through the cortical layers along the vessels. The loss of nerve cells is not restricted to one layer and is obviously dependent upon the vascular system. Figure 32*A* shows the dense cortical architectonics of the occipital lobe, but in the center of the picture there is a patchy necrosis around a capillary. Figure 32*C* gives a high power picture of the cortical cells stained by the Heidenhain iron hematoxylin method. At the right, the ground substance has a pepper and salt appearance The nuclei of the cells are dark and swollen and are surrounded by a bright halo of watery cytoplasm. At the left, these halos appear larger, and confluence of the edematous areas is recognizable. In the upper part, confluence of the halos is striking and the nerve cells have more or less disappeared. This picture is typical for almost every section from infants below the age of 9 months. In every case, edema of the fibers and loss of cells is recognizable. The cells of the substantia nigra, which is not pigmented at that age, appear well developed but are in a stage of swelling or shrinking.



Watery dissolution of nerve cells in cortex, Heidenhain iron hematoxylin stain, 5 month old mongoloid baby Marked brain edema (*D, lower right*) Perivascular necrosis with heavy calcification in white matter, 5 month old mongoloid baby Weigert myelin stain

The myelin fibers show striking pathology (fig 32*B*) Under low power the white matter appears "moth-eaten," the fibers being interrupted by numerous small patches of necrosis The vascular system is hyperemic Around many vessels, deposits of darkly stained corpuscles are recognizable (fig 32*D*). Fractions of myelin and fat substances are frequently encountered The demyelination of the cen-

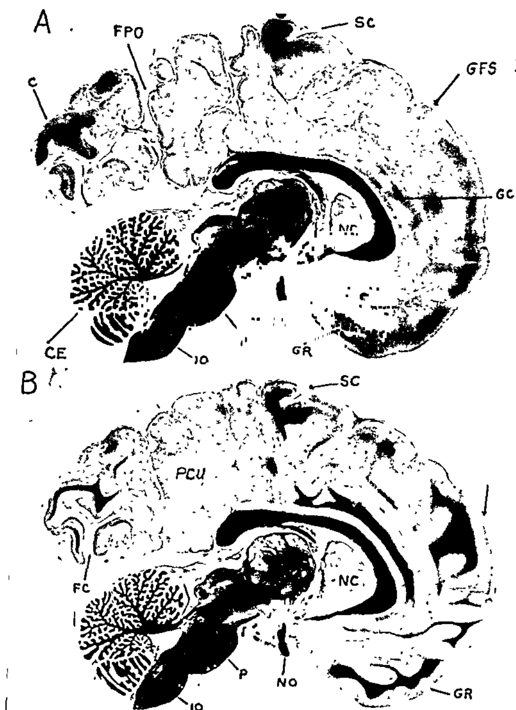


FIG. 33.—Four sagittal sections (myelin stain) through brain of female infant (2 years, 8 months, M.A. 3 months) Note retardation in formation of myelinated fibers (for details, see text).

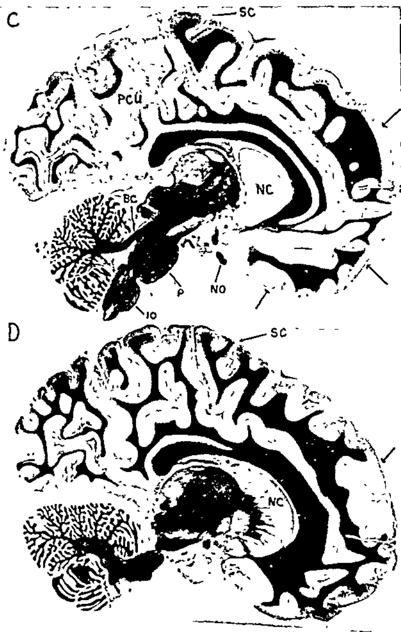


FIG 33—*Continued*

trum semiovale is striking; especially involved is the white matter of the frontal, occipital and temporal lobes; less involved are the optic radiation and the radiation of the corpus callosum, in contrast to the patchy demyelination of the association fibers.

The characteristic pathology will be further demonstrated in a number of illustrations of brain sections of infants ranging in age from 1 month 19 days to 4 years 7 months.

A most characteristic symptom of the decelerated maturation is the slowness of myelination which can be observed in certain areas of the brain and cerebellum Moreover, the myelinated radiation does not penetrate fully into the convolutions but ends at a greater distance from the convolutional peak. For orientation, figure 33 shows 4 sagittal sections through the brain of a female infant of 2 years 8 months This child did not yet sit up, stand or turn over in her crib She could only raise her head and shoulders if pulled by the hands She didn't hold toys, express affection or respond to attention

Section *A* of figure 33 is about 2 mm. lateral to the midline; such a section goes through the gray matter, and even in the normal brain of an adult, only some myelin is visible in the cortex The section shows a cerebellum small for the age, a rather large nucleus caudatus, and fairly good myelination of the thalamus, brain stem and cerebellum Some myelin is present around the central sulcus and in the cuneus However, the myelination of the precentral areas and frontal lobes lags behind that seen in normal controls An interesting aspect is the lack of fissuration which is noticeable in the whole frontal area. Of course, only a certain number of sulci are visible in any sagittal section, but figure 34 demonstrates quite clearly the disorder in fissuration and differentiation of the cortex in a comparison of cross sections through a mongoloid brain and normal controls of an even younger age This lack of fissuration deserves to be classified as incomplete pachygyria

Figure 33*B*, about 3½ mm. lateral to the first section (*A*), demonstrates some good myelination around the calcarine fissure in the occipital lobe, but at the same time more detailed observations reveal anomalies of differentiation in this area The cortex shows great underdevelopment of the myelination in the precuneus and incomplete myelination in the parietal lobes This is conspicuous even in fig 33*C*, which is about ½ cm lateral to (*B*) Figure 33*D*, about 1½ cm *lateral to the midline, shows myelination but at the same time demonstrates* again the pachygyria in the precentral areas

Figure 34 shows a comparison between the frontal lobe of a 2 year old mongoloid child and two control cases, 6 months and 13 months, respectively. Although in each of the normal sections there are areas in which the gray matter is cut obliquely, the differentiation of the cortex in (*A*) reveals the striking anomalies in differentiation of the gray matter which is duplicated and lacks fissuration in certain areas The sulci are extremely flat and sparse The band of the gray matter seems much thicker than in the norm

A particular aspect of the abnormal cortical differentiation may be seen in figure 35, in which the areas of the Betz cells, frontal lobe and inferior temporal lobe are compared with sections from two cases, 9 months and 6 months old, respectively. A comparison of (*A*) and (*D*) shows not only the striking underdevelopment of the motoric ganglion cells in (*A*) but also a general *lack of differentiation* of the nerve cells and conspicuous crowding The difference with regard

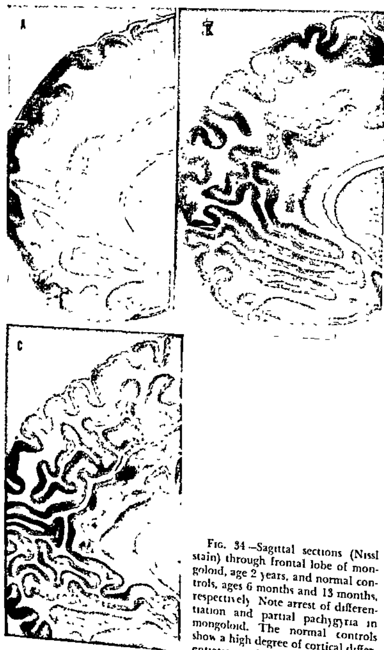


FIG. 34.—Sagittal sections (Nissl stain) through frontal lobe of mongoloid, age 2 years, and normal controls, ages 6 months and 13 months, respectively. Note arrest of differentiation and partial pachygyria in mongoloid. The normal controls show a high degree of cortical differentiation and fissuration

trum semiovale is striking; especially involved is the white matter of the frontal, occipital and temporal lobes; less involved are the optic radiation and the radiation of the corpus callosum, in contrast to the patchy demyelination of the association fibers.

The characteristic pathology will be further demonstrated in a number of illustrations of brain sections of infants ranging in age from 1 month 19 days to 4 years 7 months.

A most characteristic symptom of the decelerated maturation is the slowness of myelination which can be observed in certain areas of the brain and cerebellum. Moreover, the myelinated radiation does not penetrate fully into the convolutions but ends at a greater distance from the convolutional peak. For orientation, figure 33 shows 4 sagittal sections through the brain of a female infant of 2 years 8 months. This child did not yet sit up, stand or turn over in her crib. She could only raise her head and shoulders if pulled by the hands. She didn't hold toys, express affection or respond to attention.

Section A of figure 33 is about 2 mm lateral to the midline; such a section goes through the gray matter, and even in the normal brain of an adult, only some myelin is visible in the cortex. The section shows a cerebellum small for the age, a rather large nucleus caudatus, and fairly good myelination of the thalamus, brain stem and cerebellum. Some myelin is present around the central sulcus and in the cuneus. However, the myelination of the precentral areas and frontal lobes lags behind that seen in normal controls. An interesting aspect is the lack of fissuration which is noticeable in the whole frontal area. Of course, only a certain number of sulci are visible in any sagittal section, but figure 34 demonstrates quite clearly the disorder in fissuration and differentiation of the cortex in a comparison of cross sections through a mongoloid brain and normal controls of an even younger age. This lack of fissuration deserves to be classified as incomplete pachygyria.

Figure 33B, about 3½ mm lateral to the first section (A), demonstrates some good myelination around the calcarine fissure in the occipital lobe, but at the same time more detailed observations reveal anomalies of differentiation in this area. The cortex shows great underdevelopment of the myelination in the precuneus and incomplete myelination in the parietal lobes. This is conspicuous even in fig. 33C, which is about ½ cm lateral to (B). Figure 33D, about 1½ cm lateral to the midline, shows myelination but at the same time demonstrates again *the pachygyria in the precentral areas.*

Figure 34 shows a comparison between the frontal lobe of a 2 year old mongoloid child and two control cases, 6 months and 18 months, respectively. Although in each of the normal sections there are areas in which the gray matter is cut obliquely, the differentiation of the cortex in (A) reveals the striking anomalies in differentiation of the gray matter, which is duplicated and lacks fissuration in certain areas. The sulci are extremely flat and sparse. The band of the gray matter seems *much thicker than in the norm.*

A particular aspect of the abnormal cortical differentiation may be seen in figure 35, in which the areas of the Betz cells, frontal lobe and inferior temporal *lobe are* compared with sections from two cases, 9 months and 6 months old, respectively. A comparison of (A) and (D) shows not only the striking underdevelopment of the motoric ganglion cells in (A) but also a general lack of differentiation of the nerve cells and conspicuous crowding. The difference with regard

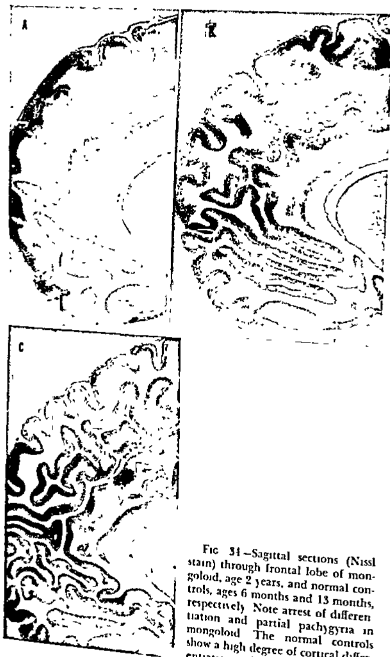


Fig 34—Sagittal sections (Nissl stain) through frontal lobe of mongoloid, age 2 years, and normal controls, ages 6 months and 13 months, respectively Note arrest of differentiation and partial pachygyria in mongoloid The normal controls show a high degree of cortical differentiation and fissuration

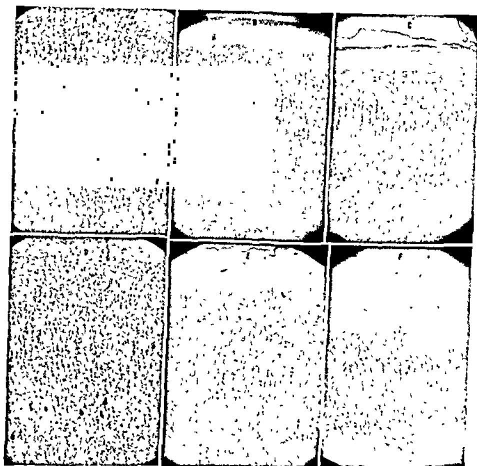


FIG 35 —A comparison of different cortical areas (Nissl stain) in mongolism and normal controls Note underdevelopment of Betz cells and cortical differentiation of the nerve cells, conspicuous crowding of embryonic cells (for details, see text)

to the crowding of the mongoloid cortex is strikingly demonstrated in comparing (*B*) and (*E*) The mongoloid cortex shows many more small, undifferentiated nerve cells which have failed to spread out, grow and form adequate connections In the normal brain of a 6 months old child, the individual nerve cells are already larger and more individualized and further apart than in the mongoloid Comparing (*C*) and (*F*), one notes the cortex to be wider in the mongoloid (*C*), the lower cortical strata, especially, are much thicker than in normal cases

This is also clearly demonstrated in figure 36, which shows three areas of the frontal lobe of a 1 month old mongoloid child (*A*) shows the abnormal cortical configuration around an abortive fissure which is surrounded by small, disorganized nerve cells (*B*) and (*C*) show again the conspicuous crowding of the gray matter with small, largely undifferentiated nerve cells

Further insight into the severe pathology of the nerve cells is documented in figure 37, in which (*A*) and (*C*) are taken from the cerebral cortex while (*B*) and (*D*) show the pathology of the cerebellum Under high magnification, all cortical cells appear in a state of severe disintegration Some nerve cells are shrunken (*A*), and a large number show a watery or homogeneous disintegration

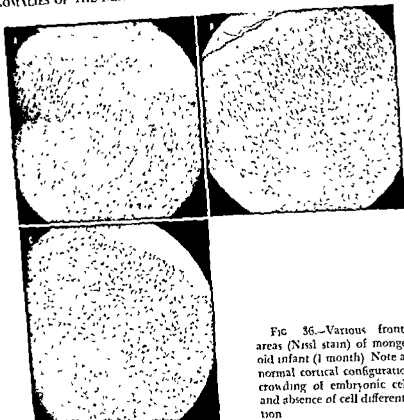


FIG 36.—Various frontal areas (Nissl stain) of mongoloid infant (1 month) Note abnormal cortical configuration, crowding of embryonic cells, and absence of cell differentiation

of the cytoplasm (C) The cytoplasm of each of these nerve cells is completely devoid of Nissl substance and is in a state of homogeneous coagulation (D) [illegible] the striking anomal [illegible] arrested in their [illegible] in the granular layer (D) shows a number of Purkinje cells in their irregular distribution and various states of degeneration Some Purkinje cells lie arrested in the granular layer At the edge of the molecular layer we find an embryonic cell layer, which is normal for that age but in mongolism persists for a longer time than in normal children

The anomalies of differentiation with the crowding of cells in the original stage of pathology are further demonstrated in figure 38 (A) shows the Betz cell layer (area 4) of a 4 month old mongoloid baby, compared with a normal control case of the same age (B) The gray stratum of the mongoloid brain seems unable to permit the nerve cells to grow and extend in space, and thus they remain in an undifferentiated embryonic stage, unable to extend and form the normal synapsis In this stage, the nerve cells are so close together that few are able to survive, and later in life we often find cortical layers which are highly depleted of nerve cells. The transitional stages of swelling, shrinkage and destruction are seen in figures 32, 37 and 41

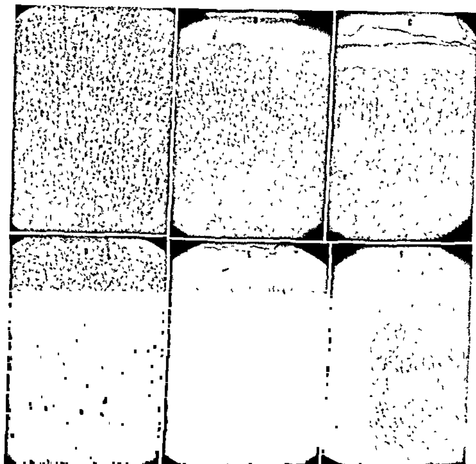


FIG 35 —A comparison of different cortical areas (Nissl stain) in mongolism and normal controls Note underdevelopment of Betz cells and cortical differentiation of the nerve cells, conspicuous crowding of embryonic cells (for details, see text).

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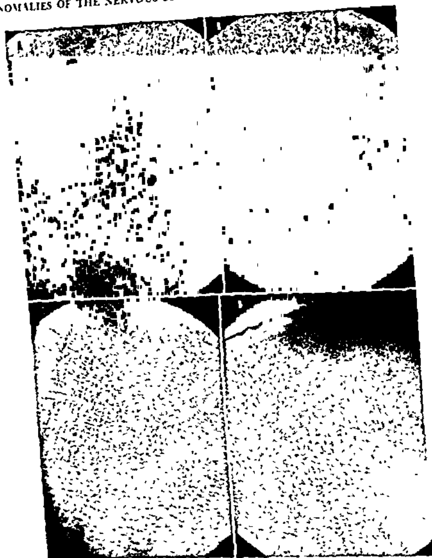


FIG. 38.—Anomalies of cell differentiation (Nissl stain) in various cortical areas (for details, see text)

Figure 39 shows another aspect of the developmental disorder of the nervous

development (C) clearly demonstrates the anomalies known as "tuber flocculus" These are undifferentiated cell piles, found in the cerebellum of more than 60 per cent of mongoloid children Apparently they go back to the earliest dif-



C) Cortical cells ap-
cells show striking pa-
id swollen (*B*, *D*) Ce
rebellum: anomalies in cell differentiation of Purkinje cells and granular layer

(*C*) and (*D*) of figure 38 contrast the calcarine fissure of a mongoloid (*C*) with a normal control (*D*). Again we see that the individual nerve cells are unable to differentiate and the brain is loaded with small embryonic cell matrices, while the individual cells in the normal have differentiated and form a clearly defined cortical stratum, typical for each functional layer.



Fig 39.—(C) "Tuber flocculus" and abnormal embryonic cell accumulation in the cerebellum

(A) In this case there is a secondary demyelination (de) of the white core, which is highly congested and shows initial stages of demyelination (B) shows the tuber flocculus in this case under high magnification

Figure 41 shows two high magnifications of the cortex (A) and (B) Both (A) and (B) show the severe Nissl disease of the nerve cells which are in a process

The Purkinje cells (C) are crowded at the margin of the granular layer, with many cells arrested in their migration The individual cells are often clumped together small and undifferentiated (D) shows a group of Purkinje cells in different stages of disintegration The cytoplasm is homogeneous, some cells are swollen some shrunken and they lie clumped together in a completely pathologic way.

Striking anomalies of the cerebellum are further demonstrated in a 4 month old baby (fig 42) (A) shows a few fairly normally spaced Purkinje cells, each one shows an undifferentiated form like that found at a younger age. The cells are lacking in differentiation and the cytoplasm is in a stage of coagulation (B) again shows the abnormal multiplication of Purkinje cell layers, with many cells clumped together In (C) and (D) the differentiation of the mongoloid cerebellum (C) is compared with a normal case of the same age (D). It is interesting to note how small the actual folia of the mongoloid cerebellum are compared with the normal The former are less than half the size of the norm Lack of extensive growth may be considered one of the reasons why the Purkinje cell layer remains crowded and the individual cell has no space for differentiation and growth

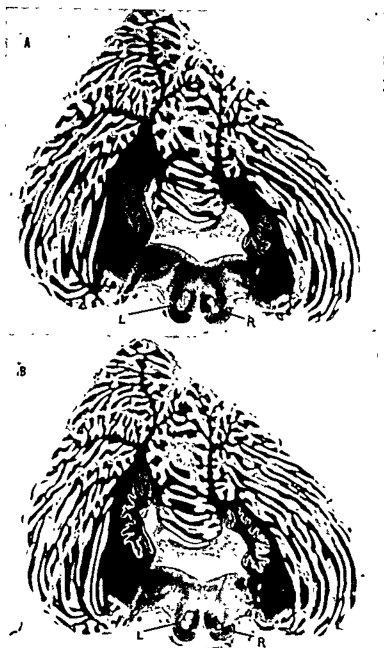


FIG. 39—(A, B) Anomalies in lateralization Note difference of inferior olivary nucleus on right and left

ferentiation of the cerebellum, at a stage of about five weeks Although the tuber flocculus (TF) may occasionally be associated with other developmental disorders of the brain, its frequent occurrence in mongolism makes it a characteristic feature of the neuropathology of this condition

Figure 40 shows a myelin stain through the frontal lobe of a 10 month old baby



FIG 39 —(C) "Tuber flocculus" and abnormal embryonic cell accumulation in the cerebellum

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cells under high magnification (*C*) and (*D*) show the cerebellum in this case The Purkinje cells (*C*) are crowded at the margin of the granular layer, with many cells arrested in their migration The individual cells are often clumped together, small and undifferentiated (*D*) shows a group of Purkinje cells in different stages of disintegration The cytoplasm is homogeneous, some cells are swollen, some shrunken, and they lie clumped together in a completely pathologic way

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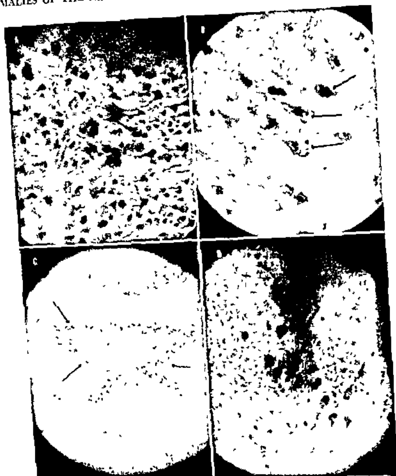


Fig 41 —(*A, B*) Abnormal cell metabolism (Nissl stain) in mongolism Note severe pyknosis and sclerosis of nerve cells in a 10 month old infant (*C, D*) Abnormal cell metabolism (Nissl stain) in cerebellum

The reported changes are not haphazard findings but consistent in every one of the brains which were studied Only the location and degree of anomalies vary to a certain extent It seems apparent that we deal here with the primary failure of the nervous system to differentiate and grow The original anlage does not appear abnormal, but at the same time that the other body organs failed to differentiate normally the brain was affected in a similar way The anomalies in the cerebellum, especially the tuber flocculus, are the most striking evidence of this arrest of differentiation. The failure of the cortex to grow and differentiate provides further evidence.

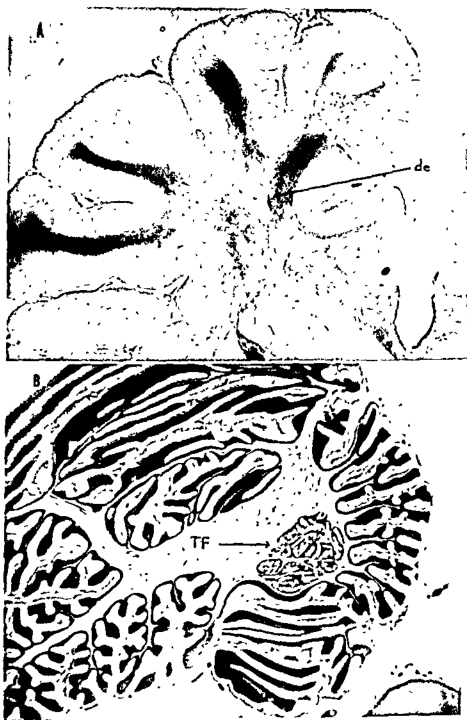


FIG. 40 —(*A*) Frontal lobe (myelin stain) Note abnormal myelination of frontal cores (*B*) "Tuber flocculus" (higher magnification)

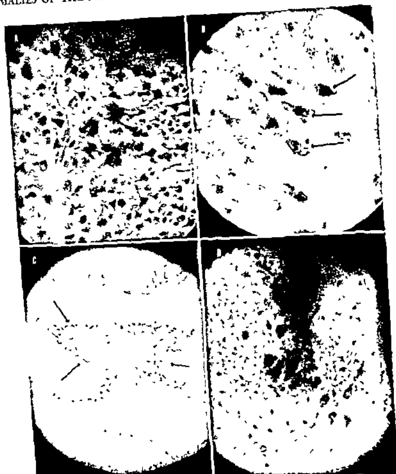


FIG 41 —(*A*, *B*) Abnormal cell metabolism (Nissl stain) in mongolism Note severe pyknosis and sclerosis of nerve cells in a 10 month old infant (*C*, *D*) Abnormal cell metabolism (Nissl stain) in cerebellum

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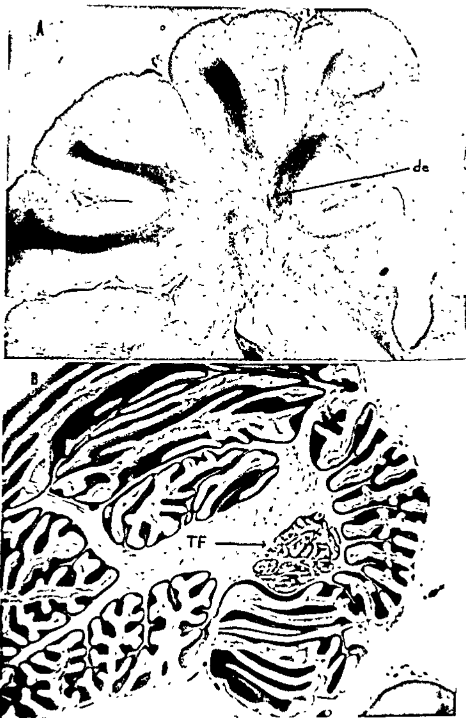


Fig. 10 —(*A*) Frontal lobe (myelin stain) Note abnormal myelination of frontal cores (*B*) "Tuber flocculus" (higher magnification)



FIG 41 —(*A, B*) Abnormal cell metabolism (Nissl stain) in mongolism Note severe pyknosis and sclerosis of nerve cells in a 10 month old infant (*C, D*) Abnormal cell metabolism (Nissl stain) in cerebellum

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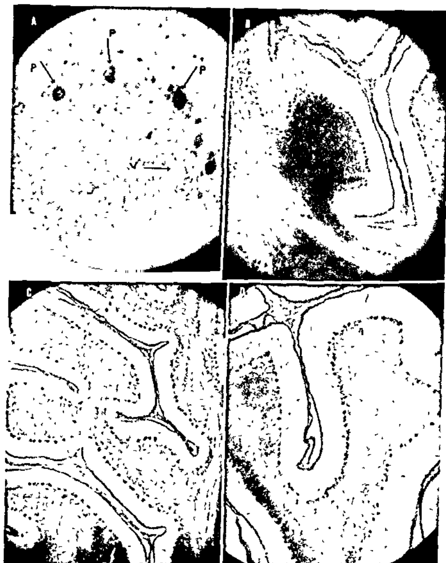


FIG. 42.—Comparison between cerebellar differentiation in mongolism and normal controls (Nissl stain) Note *crowding and underdevelopment of Purkinje cells* in mongolism, microgyria of cerebellar leaves (V, vessel, P, Purkinje cells) (Description, page 97.)

In addition to the original changes, we find degenerative processes which destroy what has been built up. In some cases it is difficult to decide whether certain myelinated fibers have ever been formed. It seems obvious that the so-called "U-fibers" are not developed to any extent (fig. 43). However, definite evidence of demyelinating processes is seen in figure 32B and D, in which the severe demyelinating process, often with deposits of calcium and secondary gliosis, is clearly demonstrated.

Fig. 43 —

SPINAL CORD

Studies of the spinal cord of mongoloids have not been published, to my knowledge For the present discussion half a hundred spinal cords were available They revealed a most characteristic picture The anomalies are identical with those seen in myelodysplasia and spinal dysraphism, indicative of a disorder of differentiation of the gray and white matter in early fetal development The spinal cord is never what one would call "normal," but the degree of pathology varies The

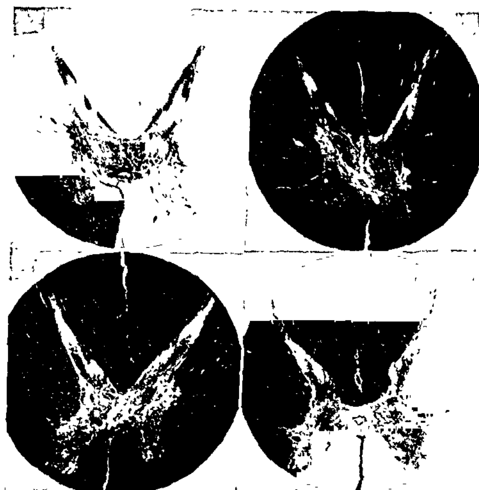


FIG. 41—(*A, top left*) Spinal cord, twelfth dorsal segment, 18 year old mongoloid boy. Note asymmetry of anterior horns: the left is underdeveloped; gliosis around central canal, absence of separation of Clark columns. (*B, bottom left*) Third dorsal segment, same case. Note asymmetry between right and left sides, with underdevelopment of all structures on the right. (*C, top right*) Eighth dorsal segment, same case. Note seam between central canal and white matter, lack of separation of Clark columns, persistent fetal configuration of gray matter with persistent roof plate. (*D, bottom right*) Upper dorsal segment, 28 year old mongoloid female. Note hypoplastic gray matter with enlarged, persistent central canal, moderate hydromyelia, gliosis of central commissure.

alterations may be divided into two groups: (1) mere retardation, ranging from hypoplasia to true fetalism, and (2) arrest of development with pathologic differentiation.

Retardation and Fetalism

It is a common feature in mongolism that the central canal remains open and forms a well outlined tube or a sagittal slot. At many



FIG 45—(*A, top*) Spinal cord, upper lumbar segment ... boy (41/58) Note ... of gray matter ... (*B, bottom*) Sp... of both poster... roof plate, lack of separation of Clark columns, ... of gray matter with persistent ... asymmetry of anterior horns



Fig 44—(*A, top left*) Spinal cord, twelfth dorsal segment, 18 year old mongoloid boy. Note asymmetry of anterior horns: the left is underdeveloped, gliosis around central canal, absence of separation of Clark columns. (*B, bottom left*) Third dorsal segment, same case. Note asymmetry between right and left sides, with underdevelopment of all structures on the right (*C, top right*) Eighth dorsal segment, same case Note seam between central canal and white matter, lack of separation of Clark columns, persistent fetal configuration of gray matter with persistent roof plate (*D, bottom right*) Upper dorsal segment, 28 year old mongoloid female. Note hypoplastic gray matter with enlarged, persistent central canal, moderate hydromyelia, gliosis of central commissure

alterations may be divided into two groups: (1) mere retardation, ranging from hypoplasia to true fetalism, and (2) arrest of development with pathologic differentiation.

Retardation and Fetalism

It is a common feature in mongolism that the central canal remains open and forms a well outlined tube or a sagittal slot. At many

recognizable. The white matter was spongy, and the vessels were congested.

Cases with only minor degrees of developmental retardation are not too frequent, but there is another more common type of developmental arrest in mongolism which seems to be unique. This is the lack of separation of the Clarke columns. In these cases, which represent the majority, the gray matter behind the central canal forms a broad mass in which the cells of the Clarke columns are embedded without being separated by white matter, as they normally are The central canal appears slotlike in a sagittal direction. The anterior horns are round and short. If the picture is compared with the embryologic development of the spinal cord, it appears that this type of pathology represents a true fetalism. The gray matter preserves the shape of the fetal gray matter. The ependymal shaft shows abnormal proliferation and abnormal differentiation. The ependymal lining is also abnormal in the brain. We see, therefore, in mongolism an abnormal differentiation of the whole ependymal shaft throughout its length from its caudal end to the lateral ventricles

Fetalism with Abnormal Differentiation

Only in about 50 per cent of the cases may the pathology be considered as a moderate or severe arrest In the other half, arrested development is associated with abnormal differentiation, certain structures fail to develop, and true malformations are present Such pathologic development consists of gliotic proliferation of the ependymal shaft with true syringomyelia and anomalies of the anterior horns, which are of different size and structure. The whole gray matter may be displaced anteriorly, so that the anterior sulcus is shallow, In one case the gray matter bordered the anterior surface of the spinal cord The [illegible]

tum [illegible]

fou [illegible] of 10 years with congenital club feet In this case a myelodysplasia of severe degree with absence of the posterior horns and abnormal differentiation of the whole gray matter was present

Study of the spinal cord provides evidence that the pathologic factors which influence the development of the fetus act from a very early period in fetal life. They interfere with the differentiation of the whole nervous system. The developmental anomalies [illegible]

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Study of the spinal cord provides evidence that the pathologic factors which influence the development of the fetus act from a very early period in fetal life They interfere with the differentiation of the whole nervous system The developmental anomalies range from moderate degrees of infantilism to severe degrees of fetalism with abnormal differentiation. The pathology includes also insufficient myelination, spongy edema of the white matter, vascular stasis and in-

sufficient myelination of the peripheral nerves. Various degrees of hydromyelia, shaft ependymosis and true syringomyelia are not rare. The most unique developmental defect is an abnormal persistence of the roof plate with junction of the Clarke columns, which are found embedded in a broad band of gray matter that forms the posterior gray commissure.

SUMMARY OF OBSERVATIONS

In spite of the fact that previous investigators were not able to reveal consistent pathology of the central nervous system in mongolism, the available material indicates that mongolism is associated with a particular neuropathology which is as typical as the clinical picture itself.

For the sake of distinction, the alterations may be divided into two groups: (1) pathology of development and (2) pathology of brain metabolism.

It has been one of the main subjects of my studies to clarify the discussion about the convolutional and fissural patterns. If the pia arachnoid is stripped off the brain and the leptomeninges are entirely removed from the sulci, it becomes obvious that the main fissural patterns are normal, and a similarity to patterns of lower animals was in no case present. All fissures which are in a sagittal direction appear distorted: they are either "S"-shaped or deviate upward, accordion-like. About the inferior and lateral parts of the frontal lobes and about the occiput, the folding is increased through upward thrust, while the convexity is stretched like an arch by shortening of the basis. It is true that the convolutions upon the convexity appear simple and broad, but an analysis of these convolutions reveals that the dividing fissures are either distorted or submerged beneath the convexity. The flattened convolutions have a drumstick shape, and fissures have disappeared by fusion of their walls. This phenomenon of fusion of the fissures is, to my knowledge, not mentioned by previous investigators, but it is one of the most characteristic features of the mongoloid brain. There was not a single brain beyond the age of four years in which this fusion of fissures was not present. Morgan has restricted his work to a study of the hypothalamic region in mental deficiency. He observed fusion of the walls of the third ventricle. In one of his cases, "The ependyma was obliterated in the center of this fused area, allowing the hypothalamus to become continuous across the midline."

In summary of the disorder of convolutional and fissural patterns, there are three factors which account for the pathology: (1) submerging of fissures through flattening and distortion of convolutions;

(2) fusion of fissures which were previously separated, (3) suppression of secondary fissures through arrest of development. In this instance, one may observe an arcade-shaped outline of the architecture; invagination of the surface has not taken place

This disorder of the "perigenisis" is not without influence upon the cortical tectonic and myelination The different cortical areas are well differentiated The disorder of the fissures, however, is associated

vestigators (Weygandt) These cells are numerous in older mongoloids. Sections which are grossly normal show rather dense arrangements of nerve cells, which correspond in their architecture to the normal after birth The infantile cortex is denser in cells and appears somewhat broader. With increasing differentiation, the space between cells becomes larger and the individual cell appears more developed In mongolism the cortex shows infantile patterns, with a broader cortical stratum and denser cell arrangement—not to speak of the cell loss, which will be discussed later.

The pathology of myelination is conspicuous in every case. Tangential fibers are either absent or poorly developed The gray matter is almost without myelinated fibers because tangential fibers are not present and the radiation does not penetrate into the superficial layers In the younger mongoloids, lack of U-fibers is conspicuous, leaving a bright band between the dark medullary core and the gray matter Especially conspicuous is the disorder and underdevelopment of myelination in the cerebellum The fibers are scarce and

myelination are absent. It is of interest to note that the disorder of cyto-architectonics and myelination is more obvious in the cerebellum, the pons and the medulla than in the pallium. Purkinje cells are lined up in several rows or are absent, and many are found arrested within the stratum granularis. A "tuber flocculus" described by Gans was seen in my material in over half of the cases studied

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was marke...
though th... ...of deterioration was not seen in all cases, minor degrees of the same alteration were frequently encountered

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From a study of mongoloid brains through all age groups, it is, therefore, evident that degeneration of brain tissue, loss of nerve cells and atrophy of the cortex with gliosis and pachymeningeal fibrosis are always present In some of my cases a coagulation necrosis was marked, with older and recent h...

...ere frequently encountered.

By demonstrating the ground substance, the speckled pepper and salt appearance of the tissue is impressive. Under lower magnifications the tissues appear mottled, thinned out and necrotic. Islands in which the ground substance seems still intact alternate with necrotic patches. On the tissue islands, nerve cells in all stages of degeneration are noticeable. The cytoplasm of many nerve cells forms a bright halo around the nucleus; the more edematous the cells are, the brighter and larger the halo In many patches these halos are confluent and form a large area of necrosis It is suggested that the dropping out of cells, recognizable in every case, is due to a continuous edematous sub merging of nerve tissue in which cell after cell meets death by suffocation. In Nissl preparations, various stages of misplacement of Nissl substance to the edge, formation of vacuoles and chromolysis are present. Many cells are loaded with fat. Similar observations are mentioned by Meyer and Jones, Canavan, and Philippe and Oberthur, who noticed vacuolated cells also It seems of importance to trace degeneration of nerve cells into its early stages, and in young mongoloids below 1 year we encounter, indeed, the first stages of this pathology. At that age the loss of cells is associated with cell changes of varying severity Acute degeneration is general and occurs within a rather densely piled cortical stratum Almost every necrosis can be traced to a vessel in the center. The material indicates that edema of the nerve tissue with asphyxiation of the cells is one of the most important pathologic features. It is, therefore, evident that the loss of ganglion cells in mongolism is due to a continuous dropping out of cells, owing to a pathologic condition of the brain. The remaining nerve cells are in a stage of severe disease, either ischemic or sclerotic, with all those changes described by Nissl, Spielmeyer, Cobb, and recent investigators of asphyxiation. In regard to the localization of cell destruction, the frontal, temporal and occipital lobes seem mainly affected, but in older mongoloids there is no part without involvement. It is, however, worth mentioning that the degeneration of the basal ganglia and the hypothalamic region is less conspicuous than the cortical destruction Especially in the mongoloid infants below one year, the cells of the hypothalamic region were well preserved, while at that age the dentate nucleus and the fascia dentata of the hippocampus showed a marked degree of disintegration.

Similar changes of a "metabolic character" are also seen in the white matter. Patchy necrosis, with softening and loss of myelination, was evident. It was again of interest to determine whether these changes are consistent with the pathology of mongolism and are present in infants below one year. Meyer and Jones included in their

material one case of a mongoloid male infant, aged 10 months They noticed some rarefaction in the myelin. There was also glia proliferation in subependymal areas and perivascular sclerosis throughout the white matter as far as it could be ascertained Davidoff included two cases of infants in his description. The first was a mongoloid female child of 11 months. In the white matter he noticed

several areas of demyelination affecting at times only a few fibers, which could be followed for a considerable distance in myelin sheath preparations Along the path of these degenerating fibers were granular corpuscles, either singly or in groups, staining brilliant red in preparations for fat and also taking the deep blue tone of the myelin fibers These areas were almost wholly confined to the neighborhood of the ventricular system A somewhat larger collection of granular corpuscles [his figure 5] seemed to differ in character from the others, the cells, in addition to vacuoles representing fat, also contained pigment which gave the iron reaction and showed a pseudo-calcareous reaction in hematoxylin and eosin preparations

In the second case, a male infant of 6 months,

numerous small areas of absent myelination were present Here also, as in Case 1, the path of the absent myelin was strewn with granular cells staining deeply for fat as well as the hematoxylin in the myelin sheath preparations

Those areas were also described by Philippe and Oberthur

A histologic analysis of the alterations in the white matter reveals that under low power the changes are best described as "moth eaten" and are areas of focal softening That the enlargement of the perivascular space is not artificial is clearly indicated by homogeneous masses which fill the spaces or fat corpuscles or calcium A network within the spaces is freqently preserved The concrements are frequently referred to as calcium or pseudo calcium because of the staining reactions Davidoff, and Meyer and Jones have analyzed those areas of necrosis and have demonstrated that they are filled with granular corpuscles and fractions taking the fat stain Meyer and Jones applied the Holzer stain and demonstrated that there is a definite scarring around the vessels The glia fibers [illegible]

ar [illegible]

by the tannin-

[illegible] appears homogeneous, and cells are difficult to recognize The venous system generally shows enlargement and congestion, stasis is marked in the capillaries of the white cores and gray matter In some cases the vascular walls are entirely homogeneous or degenerated Intima [illegible]

By demonstrating the ground substance, the speckled pepper and salt appearance of the tissue is impressive. Under lower magnifications the tissues appear mottled, thinned out and necrotic. Islands in which the ground substance seems still intact alternate with necrotic patches On the tissue islands, nerve cells in all stages of degeneration are noticeable. The cytoplasm of many nerve cells forms a bright halo around the nucleus; the more edematous the cells are, the brighter and larger the halo. In many patches these halos are confluent and form a large area of necrosis. It is suggested that the dropping out of cells, recognizable in every case, is due to a continuous edematous submerging of nerve tissue in which cell after cell meets death by suffocation In Nissl preparations, various stages of misplacement of Nissl substance to the edge, formation of vacuoles and chromolysis are present. Many cells are loaded with fat Similar observations are mentioned by Meyer and Jones, Canavan, and Philippe and Oberthur, who noticed vacuolated cells also. It seems of importance to trace degeneration of nerve cells into its early stages, and in young mongoloids below 1 year we encounter, indeed, the first stages of this pathology At that age the loss of cells is associated with cell changes of varying severity. Acute degeneration is general and occurs within a rather densely piled cortical stratum Almost every necrosis can be traced to a vessel in the center. The material indicates that edema of the nerve tissue with asphyxiation of the cells is one of the most important pathologic features It is, therefore, evident that the loss of ganglion cells in mongolism is due to a continuous dropping out of cells, owing to a pathologic condition of the brain The remaining nerve cells are in a stage of severe disease, either ischemic or sclerotic, with all those changes described by Nissl, Spielmeyer, Cobb, and recent investigators of asphyxiation In regard to the localization of cell destruction, the frontal, temporal and occipital lobes seem mainly affected, but in older mongoloids there is no part without involvement. It is, however, worth mentioning that the degeneration of the basal ganglia and the hypothalamic region is less conspicuous than the cortical destruction Especially in the mongoloid infants below one year, the cells of the hypothalamic region were well preserved, while at that age the dentate nucleus and the fascia dentata of the hippocampus showed a marked degree of disintegration.

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TABLE 6—*Weight of Thyroid in Mongolism**

Case no.	Age (Mo.)	Sex	Weight (Gm.)	Case no.	Age (Yr.)	Sex	Weight (Gm.)
1	1 5	F	1 0	12	10	F	9 8
2	2	M	2.3	13	12	F	9 0
3	5	M	1 1	14	14 5	M	7 0
4	6	F	0 5	15	15	M	6 0
5	7	M	2 5	16	16	M	7.7
6	7	F	2 0	17	16	M	11 0
7	19	M	2 0	18	17	M	5 0
				19	17	M	11 0
	Yrs.			20	18	M	3 5
8	4 5	F	1 0	21	20	M	23 0
9	8 7	F	5 0	22	20	M	19 0
10	8 8	M	2 5	23	28	F	5.5
11	9 8	F	4 5	24	31	M	3.5

* Including capsule and connective tissue

There are few careful observations on the weight of the thyroid of normal persons Hertzler in his book writes that the gland weighs 2 5 Gm at birth and 10 Gm. at an age of fourteen years The remainder of weight, say 15 grams, develops after puberty up to twenty-five grams average weight at twenty-eight years of age. For the adult thyroid, a weight of 20 to 30 Gm. is generally considered normal, and a weight of 2 to 3 Gm. is normal at birth. I am not aware of any data on the normal thyroid weight during infancy and childhood in the sea border states of the United States. For this reason I collected the weights of 40 control cases of children, and found the weights given in table 7 This table gives a reliable minimum of what may be expected in the average child, although the given weights are probably low because some feeble-minded children were included.

TABLE 7—*Average Weight of Thyroid of 40 Control Individuals*

Age in Years	Thyroid Weight (Gm.)
2–5	2–4.5
8	6
12	8–14
14	12–14
15	12–20
19	17–24
20 and above	12–27 5

CHAPTER VII

ALTERATIONS IN THE DIFFERENT ORGAN SYSTEMS

THE THYROID GLAND

When, at the end of the last century and at the beginning of this one, mongolism was recognized as a morbid entity and separated from cretinism, some interest was centered on the pathology of the thyroid. Several of the earlier reports mentioned a "normal" thyroid, apparently in contrast to the thyroid in cretinism, which shows conspicuous signs of pathology. These earlier reports had few facts to rely on as to the structure of the normal thyroid and the general patterns of endocrine pathology. In the light of present day knowledge, they are of little value Bourneville, however, reported definite changes, mostly of a degenerative nature. In recent publications, Gordon and Pennacchietti have reported pathology. The latter called attention to the similarity between goiter in childhood and the alterations seen by him in his mongoloid material. All these reports were based on only *a few observations. Thyroid therapy had been tried, but with little* success on the whole, and the function of the thyroid in mongolism is still a matter of much argument. In 1939 I first gave a report on the thyroid in mongolism, based on a study of 14 cases In the meantime, the material has increased to more than 80 cases.

The study of this material establishes beyond argument that the thyroid in mongolism is profoundly abnormal. Although the term "colloid goiter" is used to indicate the histologic appearance, it does not mean an enlargement of the glands. The weight of the thyroid is far below normal; and considering the fact that it is impossible to separate correctly the glandular tissue from the surrounding connective tissue, *the given results are still in excess of the actual thyroid* weight. The weights of 24 cases are given in table 6.

The hypoplasia is impressive at autopsy, and it is sometimes difficult to separate the gland from its surroundings. The location is rather low around the trachea, and thyroid and thymus are frequently incompletely separated.



FIG. 47.—Normal control cases for comparison (H & E stain). (*A*) Thyroid of 4½ month female infant. (*B*) Thyroid of 7 month male infant. Note well developed epithelial walls, colloid with vacuolization, and a fair amount of interstitial tissue with adequate vascular supply. Compared with the mongoloid thyroids of equal age, the difference is striking.

TABLE 8.—*"Normal" Thyroid Weights*

CHILDHOOD				
Author Place	Isenschmid Bern, Switzerland	Wegelin North Germany	Eggenberger Rome, Italy	Castaldi Florence, Italy
Age	Gm	Gm	Gm	Gm
Newborn	4-6 6	1 9	1.5-3.0	1.1
1 year	5 0	2 4	1.9	1.7
2 years	7 5	3 7	2 2	2 8
4 years	14 5	6 1	—	3 4
6 years	17 0	7.4	4.4	3 6
11 years	25.0	11.2	7.0	—

ADULTS			
Author Place	Marine & Kimball U S A	Huek, Wegelin North Germany	Marchand France
	Gm	Gm	Gm
	25	20–25	22–24

Comparison with a weight table (table 8) prepared by Eggenberger for several European countries shows that the weights given in table 6 can be generally accepted.

These tables demonstrate that the thyroids of mongoloids are extremely underdeveloped The hypoplasia varies in its extent, but it was present in all cases, with the exception of two described later. The most extreme degree of hypoplasia was seen in four patients. One mongoloid girl of 4.5 years of age had only two small nodules with a total weight of 1 Gm. In one mongoloid baby the thyroid was absent, but some abnormal thyroid tissue was found within the thymus. One 9 year old boy had a thyroid weighing 2.5 Gm , and in one 18 year old boy the gland weighed 3 5 Gm. In several cases thymus and thyroid were connected with each other, and it was impossible to separate the two without use of a microscope.

The pathology of the thyroid can be understood only through microscopic study. It may be useful to start with a brief discussion of the normal thyroid in infancy and childhood. Such a report may be the more welcome because of the lack of studies at hand.

The glandular tissue develops from solid epithelial nests during fetal life, which gradually form lumina and secrete colloid. In fetal thyroids many acini are already well developed in the last four months before birth and contain colloid. After birth the thyroid is composed of acini which are lined by cuboid or high columnar epithelium. Wet-



FIG. 47.—Normal control cases for comparison (H & E stain). (*A*) Thyroid of 4½ month female infant. (*B*) Thyroid of 7 month male infant. Note well developed epithelial walls, colloid with vacuolization, and a fair amount of interstitial tissue with adequate vascular supply. Compared with the mongoloid thyroids of equal age, the difference is striking.

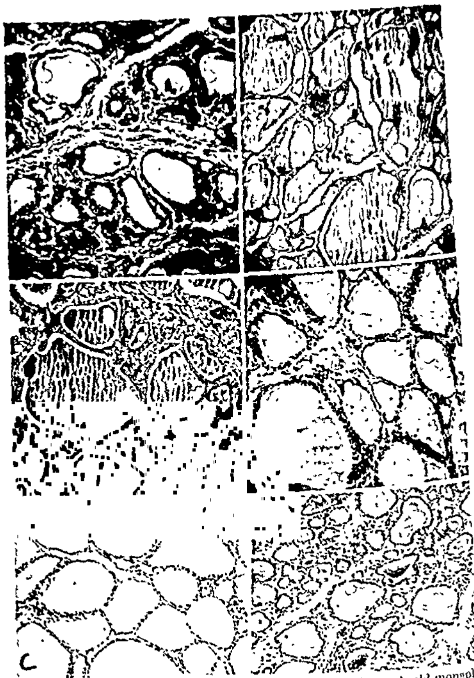


FIG. 18.—(*A*, *top left*) Colloid goiter with fibrosis in a 6 month old mongoloid female ... filled with thick, crenated colloid, flattening ... sis (*B*, *middle left*) Colloid goiter in ... e enlargement of acini up to 500 μ ... ng

of epithelial walls, ...

(*Legend continued on facing page*)

zel states that the thyroid of infants shows a uniform picture. The acini are of almost equal size, and the diameter gradually increases from 50 to 100 μ during the first year. The colloid is thin and liquid. Concerning the uniformity of the size of acini in the so called normal thyroid, my observations are more in line with those of Hertzler, who stressed that throughout infancy and childhood there are solid epithelial nests and small new-formed acini to be found beside the well developed acini which contain colloid It is, however, true that the acini gradually increase in size and that an average of 250 μ is not to be found before 4 years of life. Greater distention with flattened epithelial walls and brittle colloid is not common before the age of 8 to 12 years. The normal epithelium is cuboidal, with a vesicular nucleus and a clearly demarcated cytoplasm The adjacent acini walls do not crowd each other and are separated by a large capillary system and fine connective tissue fibers Hertzler mentions that "the colloid in very early life is so thin that it is not stained at all by eosin and only faintly by Mallory's trichrome methylene blue It does not stain normally as compared with that of the adult until the fourth to sixth year. When it does stain, it is uniformly acidophilic with eosin." Normal colloid stains red with eosin and blue with the trichrome Mallory. Hertzler and others use the term "acidophilic," but this term reminds one too much of the acidophils of the pituitary gland, which stain red both with eosin and with Mallory's trichrome stain, while normal colloid of the thyroid stains light blue with the latter If colloid becomes abnormal, thick and stagnant, the color is darker Abnormal colloid stains with the hematoxylin of the H & E stain, while it stains orange by Mallory's trichrome Brittleness is clearly indicated by wavy appearance and splintering

One may approach the problem by establishing the main patterns of pathology which can be found in infancy and childhood The so-called Basedow thyroid is not included

1. Distension of acini beyond normal size,* with flattening of epi-

* Felix Peltason in 1919 reported the great variability in size of the alveoles, which range from 20 to 180 μ The shape is irregular There is also increased proliferation of interalveolar connective tissue and epithelial proliferation (page 27)

Fig 48 (Continued)—(*D, top right*) Colloid goiter with possible toxic activity in a fifteen year old mongoloid girl Note extreme enlargement of acini filled with brittle splintering colloid, some epithelial nests between acini and papillae formation (*E, middle right*) Resting colloid goiter in a 14 year old mongoloid male Note enlargement of acini brittle colloid, flattening of epithelial walls; absence of vascularization (*F, bottom right*) Resting colloid goiter in a 7 month old mongoloid female Note flattening of epithelial walls, crenated, brittle colloid, no vascularization of interstitial tissue

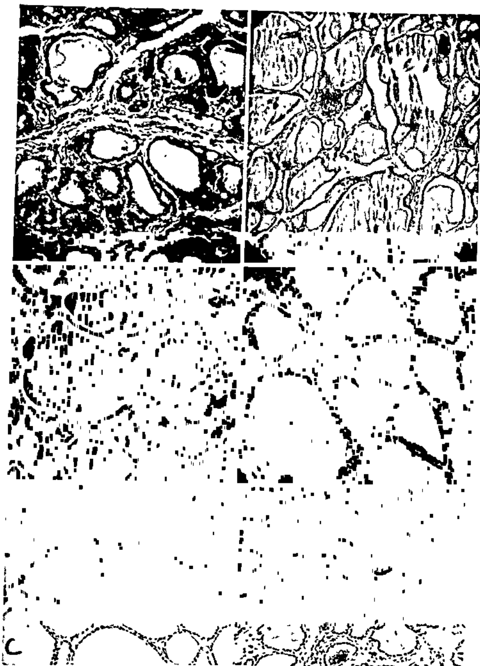


FIG 48—(*A, top left*) Colloid goiter with fibrosis in a 6 month old mongoloid female (31/62) Note enlargement of acini filled with thick, crenated colloid, flattening of epithelial walls, replacement fibrosis (*B, middle left*) Colloid goiter in an 8 year old mongoloid male (38/25) Note enlargement of acini up to 500 μ;

(*Legend continued on facing page*)

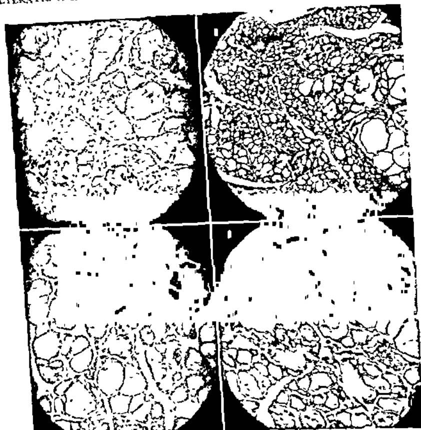


Fig 50—Thyroid in mongolism (H & E stain) (*A*) Thyroid of 20 year old female (*B*) Thyroid of 25½ year old male (*C*) Thyroid of 22½ year old male (*D*) Thyroid of 33 year old female

3. Increase in connective tissue separating the acini and encroaching upon them replacement fibrosis

4. Inequality of acini, most of them abnormally distended by colloid Solid epithelial nests and small acini with thin colloid between. Proliferation of epithelial cells in the epithelial walls, duplication of walls and papillation colloid goiter with possible toxic activity.

These four standard alterations may occur in various combinations. The pathologist is not able to make a statement about toxicity or mere hypofunction Until recently observations of pathologists and clinicians were so little in accord with each other that it seemed almost impossible to come to any agreement Recent research, however, gives a lead for a sounder approach to correlating histology and physiology. The cells of the thyroid are a secretory epithelium and have the task

thelial walls, disappearance of cytoplasm border lines, and pyknosis of nuclei. Acini tightly filled with colloid which stains dark pink or dark blue and orange and is wavy and brittle. The epithelial walls touch each other, and there is little interstitial tissue: colloid goiter, "resting."

2. Absence of colloid formation. The acini are small and empty, or no lumina are formed at all. Parenchyma consists of solid epithelial nests: fetal gland, developmental arrest or retardation

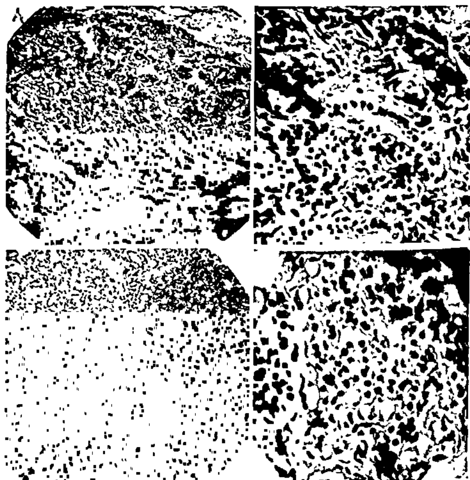


Fig 49—(*A, top left*) Colloid-free "cretinoid" thyroid in a 9 day old mongoloid male baby (31/76) Note fetal nodule without formation of acini and colloid, increased connective tissue and irregular epithelial proliferation (*B, bottom left*)
Note
loid-
regu-
lar epithelial proliferation without acini formation, increased fibrosis (*D, bottom right*) Colloid-free "cretinoid" thyroid in 11 year old mongoloid (44/139) Note "myxedema" cells without colloid formation in thyroid

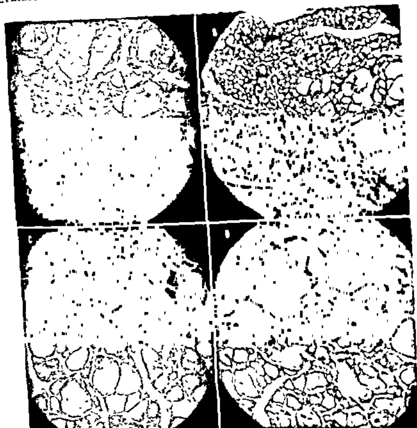


FIG 50 —Thyroid in mongolism (H & E stain). (*A*) Thyroid of 20 year old female (*B*) Thyroid of 25½ year old male (*C*) Thyroid of 22½ year old male (*D*) Thyroid of 33 year old female

3. Increase in connective tissue separating the acini and encroaching upon them replacement fibrosis.

4 Inequality of acini, most of them abnormally distended by colloid. Solid epithelial nests and small acini with thin colloid between Proliferation of epithelial cells in the epithelial walls, duplication of walls and papillation colloid goiter with possible toxic activity

These four standard alterations may occur in various combinations The pathologist is not able to make a statement about toxicity or mere hypofunction Until recently observations of pathologists and clinicians were so little in accord with each other that it seemed almost impossible to

lead for a

The cells

thelial walls, disappearance of cytoplasm border lines, and pyknosis of nuclei. Acini tightly filled with colloid which stains dark pink or dark blue and orange and is wavy and brittle. The epithelial walls touch each other, and there is little interstitial tissue: colloid goiter, "resting."

2. Absence of colloid formation. The acini are small and empty, or no lumina are formed at all. Parenchyma consists of solid epithelial nests. fetal gland, developmental arrest or retardation.

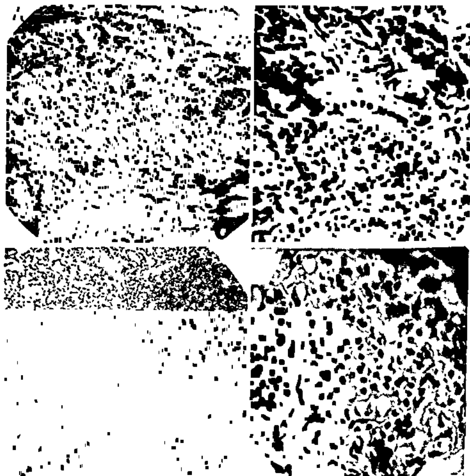


Fig 49—(*A, top left*) Colloid free "cretinoid" thyroid in a 9 day old mongoloid male baby (31/76) Note fetal nodule without formation of acini and colloid, increased connective tissue and irregular epithelial proliferation (*B, bottom left*) [illegible] Note [illegible] Colloid- [illegible] irregular epithelial proliferation without acini formation, increased fibrosis (*D, bottom right*) Colloid free "cretinoid" thyroid in 11 year old mongoloid (41/139) Note "myxedema" cells without colloid formation in thyroid

be determined. Myxedema cells were present in some of these glands; the lack of colloid was conspicuous in all of them.

The presented material provides evidence that approximately 18 per cent of the mongoloid patients, especially babies and infants, are on the threshold of hypothyroidism and suffer from an inadequate thyroid supply. In all mongoloids, thyroid function is lagging even if it cannot be demonstrated by available physiologic tests. The only gland which was macroscopically enlarged was that of a patient with Hashimoto's thyroiditis, in which practically the entire gland was replaced by lymphatic tissue. Of the two "normal" glands, one was that of an 8 month old baby who died of pneumonia after having been treated for seven months with thyroid and pituitary injections; the other was that of a 2 day old mongoloid. The gland in the latter case showed well developed, rather large acini which contained thick colloid. This is not exactly what one may consider a normal thyroid and is suggestive, at least, of some abnormal premature stimulation.

I may summarize that the mongoloid baby starts life with abnormal thyroid function. Not only is such a thyroid not fit to provide the necessary hormones, but the fact that the thyroid shows profound pathology from the very beginning indicates that the causative factors operate from the prenatal period on. It would be of great interest if one could draw conclusions from the pathology of the newborn as to the maternal deficiency, but the observations are still too confusing.

The histologic observations indicate a definite thyroid pathology in mongolism. Research over the last decades has established a useful concept of multiple interrelated parameters of thyroid function. Various steps in the course of thyroid function are determined by tests presently available, and each test throws light on an individual parameter. Some test results are reported in chapter VIII. As will be seen, some parameters in the thyroid function of the mongoloid patient are normal; but the fact that some intermediary steps do not reveal abnormal function does not permit the conclusion that the whole gl...

* For further information, see the comprehensive review of "The thyroid gland" by Hamolsky and Freedberg, New England J. Med., which appeared in January 1960, after completion of this chapter.

TABLE 9.—*Pathology of Thyroid in Mongolism*

	No	%
Colloid goiter, "resting"	15	27 3
Colloid goiter with marked fibrosis	16	29 1
Colloid goiter with signs of possible toxic activity	11	20 0
Fetal glands without colloid formation	6	10 9
Fetal cell nests and nodules with some colloid formation in periphery	4	7 3
Chronic lymphatic thyroiditis (Hashimoto's thyroiditis)	1	1 8
Normal (one prematurely advanced)	2	3 6
	55	100

of discharging their secretion into the lumen of the acini, in which the incretion is stored as colloid The colloid is viscous, but it is a *fluid that is in permanent exchange with the epithelial wall, which* absorbs certain agents as well as produces new material It is easily understood that in order to function there has to be a normal epithelial wall, colloid in a correct state of liquidity, and sufficient vascularization. If colloid is stored and petrified to such an extent that the epithelial wall is flattened and the cells are unable to secrete, the gland is no longer sustaining normal function. If no acini are formed and no *colloid* is produced at *all*, the *gland* is *then* unable to carry out its assignment. The deduction that new growth of epithelium may have a toxic influence upon the organism is taken from observations in Graves' disease, in which epithelial proliferation and papillation dominate the picture. The type of toxicity and its extent cannot be determined by histologic means

The pathology of the thyroid in mongolism is summarized in table 9

The mongoloid has a thyroid which does not function properly. If we take all cases with resting colloid goiter and fibrotic colloid goiters or those with possible toxic activity, we see that 42 of the 55 patients fall into this group Histologically, the increased colloid storage is undoubtedly the most frequent finding in mongolism and may be seen even in babies of a few months. Such completely resting colloid thyroids have never been described in infants of such a young age. It is wrong, however, to consider the colloid accumulation as the only type of pathology present in mongolism It is important to realize that 10 patients, or 18.2 per cent, had fetal glands which were either not developed at all or showed fetal nodules of considerable size Whether this fetal tissue as such exercises any abnormal toxic influence cannot

be determined. Myxedema cells were present in some of these glands; the lack of colloid was conspicuous in all of them.

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[illegible] in the discharge [illegible] efficiency upon peripheral tissues. Evidence points to the fact that the *hormonal* interplay with the other tissues and glands is abnormal.*

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THE PITUITARY BODY

Observations on 54 cases of mongolism, in which a careful histologic study of the pituitary was made, indicate two patterns of alterations:

1. An underdevelopment and deficiency of chromophobic cells, and apparently an inability to form chromophilic elements
2. A definite shift toward the accumulation of eosinophilic granules and basophilic elements in limited areas while chromophobic elements are inconspicuous.

Both types of alterations reveal deficiency in the secretory activity of the anterior pituitary lobe. The chromophobic cells are the predominant element in infancy and childhood, and are generally considered the precursors of the eosinophilic and basophilic cells In many cases of mongolism, the chromophobic elements in the pituitary are underdeveloped or in a stage of degeneration. The anterior lobe is congested, the vascular spaces enlarged and the chromophobic cells pyknotic.

Much more common, however, is the surprising observation that the pituitary is loaded with eosinophilic cells. In the majority of these cases, very few chromophobic and basophilic cells were found In other cases, both eosinophilic and basophilic cells were present, but the chromophobes were inconspicuous. Similar observations were reported by Felix Peltason in 1919. He mentions that "both forms of chromophils seem increased in contrast to the chromophobic cells, but especially the eosinophilic, which form whole strands and islets. In contrast, the number of chief cells appears reduced."* Expressed in percentages, the cell counts indicate that eosinophils may be present in more than 80 per cent, which indicates a definite shift toward eosinophilia In these cases the absence of chromophobes was as remarkable as the alterations found in the basophils These showed either regression toward a large, stainless chromophobic cell (delta cell, fig 51*C*) or were unusually heavily stained and enlarged, revealing vacuolation This type of basophil is known as a "castration cell" (fig. 51*D*). Thirty cases, or 55 6 per cent of the material, showed this type of pathologic shift In four instances, no outstanding alterations could be observed. These cases showed a fairly normal distribution of the three cell types.

The patterns of pathology of the pituitary in mongolism suggest a chronic pituitary deficiency All endocrine glands show the effect of this deficiency.

The observations in mongolism indicate that group 1, the chromophobic regression with or without delta cells, reflects the hypothyroid-

* Translation by the author, from *Zur Kenntnis des Mongolismus*, page 30.



FIG 51 —(*A, top, left*) Pituitary of a 5 month old mongoloid male (37/6) Note

(37/10) Note large chromophobes, "delta cells" also described as struma cells (Romeis), thyroprival cells (Kraus) Cytoplasm grayish-blue, dust like. (*D, bottom right*) Pituitary of a 20 year old mongoloid male Heavy basophils with vacuolation, "castration cells"

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FIG. 51 —(*A, top, left*) Pituitary of a 5 month old mongoloid male (37/6) Note complete eosinophilic shift with absence of chromophobes (a) alpha cells or acidophiles (bl) blood in enlarged spaces (*B, top right*) Eosinophilic shift in a 7 month old female baby (37/1) (a) alpha cells or acidophiles, (bl) blood Note absence of chromophobes (*C, bottom left*) Pituitary of a 12 year old mongoloid female (37/10) Note large chromophobes, "delta cells" also described as struma cells (Romeis), thyroprival cells (Kraus) Cytoplasm grayish blue, dust like (*D, bottom right*) Pituitary of a 20 year old mongoloid male Heavy basophils with vacuolation, "castration cells"



FIG 52 —Pituitary in mongolism (Mallory-Masson stain) (*A*) Horizontal section through pituitary of 4 year, 3 month old mongoloid male (*Below* the kidney-shaped anterior lobe shows large area of whitish cells, indicative of eosinophil Some colloid storage in the Rathke pouch *Above* the posterior lobe is fibrotic, with very few pituicytes) (*B*) Horizontal section through anterior lobe of 4 year, 7 month old female mongoloid Both lateral fields are exclusively eosinophilic. The center field contains undifferentiated chromophobes

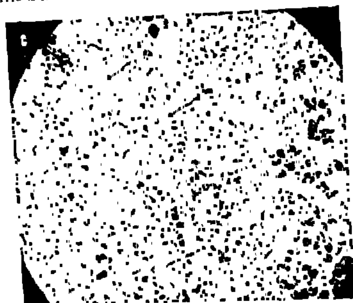


FIG 52—(C) Anterior pituitary cells, 9 year 5 month old male mongoloid *Note* complete eosinophily (e)

hypogonadal type; and group 2, the shift toward chromophilia with or without castration cells, is influenced by the colloid stasis of the thyroid. Although the relationship between colloid goiter and acidophily is not 100 per cent, of 35 cases with colloid goiter, 26 showed increased eosinophilia On the other hand, of the colloid-free thyroid cases, only 1 showed this shift toward eosinophilia of the pituitary, and it is quite possible that some parts of the thyroid contained unrecognized amounts of colloid

The observation on the pituitary, that there is a shift toward eosinophilia, came originally as a surprise because eosinophils are considered the producer of growth hormones, and gigantism and acromegaly are associated with eosinophilic tumors. It therefore seems paradoxic to find in a growth deficiency like mongolism a large accumulation of eosinophilic cells in the pituitary An analysis of the facts reveals, however, that this type of chromophilic storage fits well into information gained recently through experimentation and clinical observations. The eosinophilic shift is apparently a symptom of thyroid and gonadal dysfunction and is associated with colloid stasis in thyroid and pituitary. Not only has this eosinophilic shift been observed in other cases of dwarfism, but it is worth noticing that the only control cases that showed alterations in the liver similar to those seen in mongolism also showed extreme colloid accumulation in the



Fig 52.—Pituitary in mongolism (Mallory-Masson stain) (*A*) Horizontal section through pituitary of 4 year, 3 month old mongoloid male (*Below* the kidney-shaped anterior lobe shows large area of whitish cells, indicative of eosinophil. Some colloid storage in the Rathke pouch *Above* the posterior lobe is fibrotic, with very few pituicytes) (*B*) Horizontal section through anterior lobe of 4 year, 7 month old female mongoloid Both lateral fields are exclusively eosinophilic The center field contains undifferentiated chromophobes

settled, but strong suspicion pointed to the woman's father (blood group examinations!). The child was observed at a children's hospital at 6 months of age, where her appearance was considered unusual but not indicative of mongolism. (The reproduced photographs of the child definitely seem to exclude mongolism.) The child had a slight epicanthus and a somewhat sunken nose bridge but no other mongoloid stigmata At the age of 5, severe retardation of mental development was obvious The child "cannot stand or walk, does not talk." No toilet training had been achieved. "The development is much stunted; she measures only 89 cms. in length and weighs 10.5 kilogrammes" The head was microcephalic, "circumference 46 cms." (pages 537–538)

Histologic studies of the testes and ovaries of patients with mongolism are rare.

The Male Gonads

Twenty six cases were available for microscopic study, with ages ranging between 2½ months and 31 years There were 9 cases in the age group below 2 years, 5 of which may be considered within normal range for that age group The seminiferous tubules were filled with Sertoli cells, among which one to three spermatogonia or spermatogenic cells were found per tubule. In one case the interstitial tissue [illegible]

[illegible] were lined with Sertoli cells The interstitial tissue consisted of more or less coarse fibrous tissue, which was in some instances greatly increased In no case were interstitial cells found.

The second group of cases comprised 8 patients between the ages of 4 years 5 months and 15 years 10 months. In all these instances the anatomic picture was very uniform. The testicles were very small and undersized, measuring between 10 and 17 mm. in length and 6 to 8 mm in width, on cross section The histologic picture showed small seminiferous tubules filled with Sertoli cells without spermatogenic cells The interstitial tissue consisted of coarse strands of fi[illegible]

[illegible] years of age.

[illegible] group two patterns of pathology were found. No complete maturation, however, was found in any instance In measuring the size of the testes, it was obvious that 3 cases showed a better development, which corresponded to about two-thirds of the normal size of a male testicle, which is about 5 cm in length and 3½ cm. in width,

pituitary cleft and tubules. This stasis has also been observed in some cases of cretinism. We are therefore entitled to conclude that eosinophilia as such is not a sign of increased growth hormone production but a sign of secretory stagnation. In this group of mongoloid patients, the accumulation of storage material indicates a deficiency of growth action. The fact that eosinophils and basophils may be present, independent of the other type and also without full development of the chromophobes, provides further evidence that each of these three cell types adds certain agents to the general pituitary secretion. Under pathologic conditions, this unison of action is split. Normal function requires a delicate coordination of all cell systems, not only within the anterior pituitary body but within the whole endocrine milieu.

Emphasis has been placed upon the secretory pathology of the anterior pituitary lobe because observations indicate the importance of a dysfunction of this system. *This, however, does not mean that the* posterior lobe is completely normal and that the nervous regulation is without importance.

THE GONADS

Anomalies in sex development of mongoloid males and females are common. More than half of all male children have only one testicle descended or none. The scrotum and penis are often underdeveloped or abnormal. Female infants often have anomalies (described in the clinical section). In untreated girls, menarche is often delayed and the menstrual cycle irregular; menopause starts early. Heterosexual interest is rarely present in mongoloid boys, but masturbation may be observed—especially if other children have initiated the mongoloid boy. It is not yet known whether male adults with mongolism could fertilize, but there are a few known cases of mongoloid girls in whom pregnancy occurred.

In 1949, Grace Sawyer reported the first confirmed case of a mongoloid having given birth to a normal child. The mother, short in stature (4 feet 7½ inches), obese, having coarse rough skin, eyes slanting with epicanthal folds, IQ 25, had been delivered of a female infant, weighing 2532 grams, by Cesarean section in 1937. The child had been tested throughout childhood and adulthood and had scored IQ's of over 120. She is now married and has a normal child.

On the other hand, two confirmed cases have been observed in the United States in which mongoloid girls have been impregnated by relatives and have given birth to a mongoloid child.

R. Schlaug in 1958 reported a case in which a typical mongoloid woman gave birth to a child at the age of 20. Paternity was never

Sertoli syncytium, and little or no spermatogenic tissue was present. In some cases the basal membrane was greatly thickened. The interstitial tissue consisted of more or less coarse masses of fibrous tissue with no interstitial cells. All these cases showed a high degree of testicular hypoplasia and degeneration

There are several points of considerable interest in the pathology of the male gonads in mongolism. It is noteworthy that in the baby group several cases were found within normal range, indicating that some mongoloids at least have fairly normal gonadal equipment at birth The degeneration which is seen in the older age groups seems, therefore, to be due to the absence of those factors which are necessary to develop and stimulate gonadal function to maturity. The absence of spermatogenic tissue in other cases, however, confirms the observation that some of the children are so severely damaged in the prenatal period that germinal epithelium never differentiates. This observation is further confirmed by the large number of mongoloid boys with undescended testicles *It is somewhat surprising to see that* in the second age group, in those boys who died before puberty, all testicles showed a great amount of atrophy and degeneration. The infectious diseases to which these children succumbed may possibly have added to the picture of complete testicular atrophy. The last group

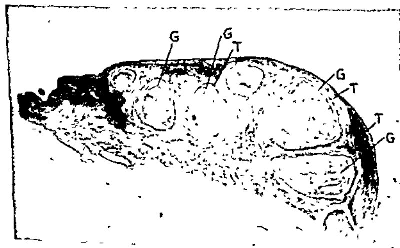


FIG 53—(*D, at b*...
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on cross section. Three testicles measured 3 × 1.8 cm., 2.8 × 1.6 cm., and 3 × 1.6 cm., respectively. In these instances some spermatogenic activity was noticeable. The tubules were lined by Sertoli cells, and numerous mitotic figures were recognizable in the spermatogonia. *None of the cases, however, showed mature sperm cells. The interstitial* tissue contained a few interstitial cells; it was rather fine and loose and not markedly increased, with the exception of the second case, in which a partial fibrosis was noticeable. These 3 cases may be grouped as "almosts" The development, however, lagged definitely behind normal maturation.

The remaining 6 cases showed again a rather uniform picture. The *small testicles measured between 20 and 23 mm. in length and 8 to 12* mm. in width. The seminiferous tubules were small and filled with a

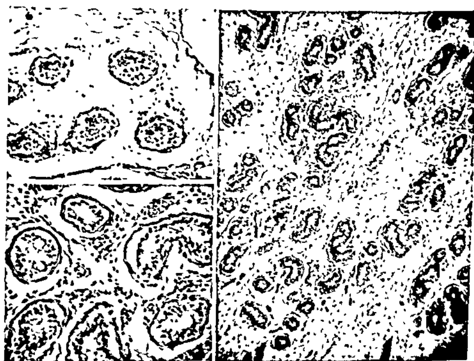


FIG. 53.—(*A, top, left*) Gonads in mongolism Testicular atrophy of a 16 year old mongoloid The seminiferous tubules contain only degenerated Sertoli cells which [illegible] ...ase in interstitial [illegible] ...sent (*B, bottom* [illegible] ...ing of the base- [illegible] ...nic cells No in- [illegible] ...baby Note the [illegible] ...he tubules from [illegible] ...eral tubules still contain "germinal epithelium" embedded in the Sertoli syncytium

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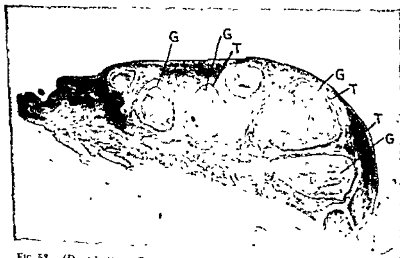


FIG 53 —(*D, at bottom*) Ovary of a 19 [illegible]

of cases offers for the first time the opportunity to study the various patterns of gonadal deficiency in man in connection with the other endocrine glands.

Gonadotropic hormones have been fractionated into the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). Both factors are best extracted from the pituitary tissue by alkaline solvents Both fractions show definite differences in solubility, the LH fraction being not readily soluble below a pH of 5, while FSH is soluble over a wide range of pH and is extracted by aqueous solvents whether basic or acidic This observation probably offers the key to the problem of acidophilic and basophilic granules in the pituitary cells. Although the usual dyes are not strictly acid or basic in a chemical sense, their pH differs to some extent.

Experiments in male rats by Greep, Fevold, Hisaw, and many others have shown that the FSH factor stimulates only tubular development, leaving the interstitial elements unaffected. The LH factor, on the other hand, has a definite influence on the interstitial tissue, while the germinal epithelium remains unaltered Growth of the gonads seems to depend on the presence of both factors If only FSH is used, a slight increase in size occurs, while the LH factor has little influence upon augmentation. If both hormones are present to a certain degree, normal augmentation will take place.

These observations are of great interest with regard to the pathologic patterns of atrophy in man. I have called attention to the fact that the pituitary in mongolism shows two main types of pathology: (1) a chromophobic shift without development of chromophilic elements, and (2) a chromophilic shift with absence of chromophobic elements. In comparing the pituitaries with the gonads, it is conspicuous that the patients with inability to form chromophilic elements show definite gonadal hypoplasia and atrophy. None of the cases with only chromophobic cells in the pituitary showed any degree of normal development in the gonads. Conversely, a chromophilic shift warrants a better gonadal development in the majority of cases, although the presence of chromophilic elements may not prevent degeneration in every case. A rather definite relationship between these factors is observable in patients after puberty, and it is possible to predict the condition of the gonads from a study of the pituitary. Patients with infantile chromophobic cells show gonadal atrophy and hypoplasia, and one may conclude that the chromophobic elements of the pituitary are not able to maintain any degree of gonadal activity. The best development of the testicles was present in those patients in whom alpha and beta cells were fairly numerous. Cases which showed only alpha

cells had some activity of the spermatogenic epithelium but, at the same time, increased fibrosis of the interstitial tissue. On the other hand, the presence of beta cells guarantees fair development of the interstitial tissue, while tubular activity demands the presence of alpha cells. One may therefore conclude that these observations provide evidence of the direct relationship between gonadal activity and chromophilic cells. It is suggested that the alpha cells provide the FSH fraction, while the LH fraction is provided by the beta, or "basophilic," cells. Acromegaly and hyperthyroidism are both associated with an increase in acidophilic cells in the pituitary and a temporary increase in gonadal activity.

Mongolism and cretinism are associated with hypopituitarism. If all chromophilic elements are absent, gonadal hypoplasia is conspicuous. If alpha cells are present, but beta cells are missing, tubular activity is present to a certain degree, but no maturation occurs. If beta cells are present but alpha cells are absent, the interstitial tissue is fairly well preserved but tubular activity is missing. Thus, a definite relationship between alpha and beta cells and the gonadotropic fractions in man seems [illegible]

[illegible] ps before
p[illegible] between
p[illegible] observed.

The Female Gonads

[illegible]

ou[illegible]

fa[illegible] major labia appear sometimes like round cushions or are hypertrophic. After puberty, development of secondary sex characters is abnormal. Mongoloid girls mature late, and menstruation may not start before the end of the teens. The breasts remain infantile longer than in normal children, although they frequently become very heavy and pendulous owing to abundant fat development. The [illegible] glands a[illegible]
females [illegible]
alies in [illegible] secretory glands which participate in developing sex characteristics (ovaries, adrenals).

It is not surprising, therefore, that the ovaries of mongoloid patients were often found abnormal, with the exception of some babies whose ovaries were within normal range. This indicates, again, that the primary development is not necessarily abnormal, and the pathology which is found in older mongoloids is due to lack of stimulation and maturation, which is supported by action from other glands. Hy-

of cases offers for the first time the opportunity to study the various patterns of gonadal deficiency in man in connection with the other endocrine glands.

Gonadotropic hormones have been fractionated into the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). Both factors are best extracted from the pituitary tissue by alkaline solvents. Both fractions show definite differences in solubility, the LH fraction being not readily soluble below a pH of 5, while FSH is soluble over a wide range of pH and is extracted by aqueous solvents whether basic or acidic. This observation probably offers the key to the problem of acidophilic and basophilic granules in the pituitary cells. Although the usual dyes are not strictly acid or basic in a chemical sense, their pH differs to some extent.

Experiments in male rats by Greep, Fevold, Hisaw, and many others have shown that the FSH factor stimulates only tubular development, leaving the interstitial elements unaffected. The LH factor, on the other hand, has a definite influence on the interstitial tissue, while the germinal epithelium remains unaltered. Growth of the gonads seems to depend on the presence of both factors. If only FSH is [illegible] the LH factor has little in- [illegible] ies are present to a certain [illegible] e

These observations are of great interest with regard to the pathologic patterns of atrophy in man. I have called attention to the fact that the pituitary in mongolism shows two main types of pathology: (1) a chromophobic shift without development of chromophilic elements, and (2) a chromophilic shift with absence of chromophobic elements. In comparing the pituitaries with the gonads, it is conspicuous that the patients with inability to form chromophilic elements show definite gonadal hypoplasia and atrophy. None of the cases with only chromophobic cells in the pituitary showed any degree of normal development in the gonads. Conversely, a chromophilic shift warrants a better gonadal development in the majority of cases, although the presence of chromophilic elements may not prevent degeneration in every case. A rather definite relationship between these factors is observable in patients after puberty, and it is possible to predict the condition of the gonads from a study of the pituitary. Patients with infantile chromophobic cells show gonadal atrophy and hypoplasia, and one may conclude that the chromophobic elements of the pituitary are not able to maintain any degree of gonadal activity. The best development of the testicles was present in those patients in whom alpha and beta cells were fairly numerous. Cases which showed only alpha

those enlarged follicles were easily recognizable by the naked eye. The cortex was small and contained few primordial follicles. The enlarged follicles were lined by the interna and a well preserved membrana granulosa. The latter was lifted from the theca on some points and floating, but not degenerated. No ova were found in these follicles. The picture indicates that follicle stimulation had taken place, but the agents which bring about degeneration of the follicles must have been missing and involution did not take place.

In the third group another phenomenon was conspicuous. There were no cysts. The whole stroma was filled with atretic corpora lutea, in which the lutein cells were still recognizable, although they had no nuclei and were without lutein. While normally the atretic corpora lutea become connective tissue scars which take little space within the stroma, in these ovaries numerous large atretic bodies which had failed to undergo complete involution were found.

It is quite obvious that the two patterns of pathology seen in the second and third groups represent two separate types of gonadotropic deficiency. It is suggested that in the second group follicle stimulation is present, but no luteination takes place. In the third group no follicle stimulation is seen, but the LH is operating and preventing complete disappearance of the atretic corpora lutea.

THE SUPRARENAL GLANDS

Anatomy and Postnatal Development

is well es-

Addison's

the adrenals in childhood have been the subject of only a few investigations, and the role of the adrenals in growth disorders is practically unknown. It seems, therefore, worth-while to give first a brief outline of the anatomy and a short review of the problems under discussion.

The adrenals consist of cortex and medulla. The cortex surrounds the medulla as a fruit does its kernel. Beneath the capsule a narrow cortical zone is found, which is called the zona glomerulosa. This layer consists of small columnar cells closely packed in ovoid groups or in nests which rest upon the next zone like caps. The nuclei stain deeply, and the cytoplasm is rather scanty. Beneath the zona glomerulosa are found columns of epithelial cells which form the zona fasciculata. This zone constitutes the widest portion of the cortex and consists of polyhedral cells which are larger than those of the

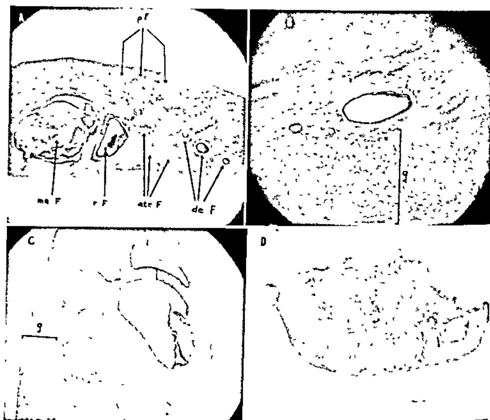


FIG 51—The ovary in mongolism (H & E stain) (A) 5 month old female. Note numerous larger and smaller corpora lutea and growing follicles (pF, primary, ma, mature, r, ripe, atr, atretic, de, developing), varying in size up to 4 mm diameter. Cortex filled with primary ova (B) 3 year, 11 month old female Note fairly adequate cortex with primary ova The stroma is filled with smaller and larger cysts, maturing ova and corpus luteum scars (g, germinal layer) (C) 2 year, 8 month old female Note cortex with thin layer of primary ova (g, germinal layer) Huge cysts and scars in stroma (D) 33 year old female Note almost complete degeneration of primary ova The fibrotic stroma is filled with scars and cysts of various sizes

poplasia of the ovaries was present in all cases, and no mongoloid female was found with ovaries of normal size. The pathology falls into three groups: (1) general hypoplasia without activity of the germinal epithelium; (2) hypoplasia with tendency to persistence of follicular cysts and lack of involution; (3) hypoplasia with little follicular activity, but tendency to persistence of atretic corpora lutea

The hypoplastic, "resting" ovaries are small bodies with a limited number of primordial graafian follicles, many of them degenerated. No mature stages are found. The fibrous stroma is increased.

The ovary of the second group is characterized by the presence of numerous large follicle cysts. In an ovary of a 12 year old

tex of other authors. The penetration takes place from the medial and caudal surface in groups and strands, until the future medullary cells are piled near the central vessels inside of the fetal cortex. Differentiation of sympathicogenic cells into chromaffin cells takes place mainly after birth, but the immigration is closed long before that time. At birth we find, therefore, three different layers, which enclose each other, fruitlike (1) the permanent cortex, (2) the fetal cortex or "central body," and (3) the medulla. We shall see that penetration of medullary cells through the cortex and central body is sometimes arrested, and funnel-shaped bundles of medullary cells may be found within the cortex or even outside, resting upon the capsule. These medullary cells, which apparently came too late and found immigration closed, may form the center of isolated settlements around the capsule and form accessory bodies, which are extremely numerous in mongolism In other instances the cortex alone is separated into smaller nodules, which contain all types of cortical cells but no medulla.

Development of the human adrenal in postnatal life is associated with a unique involution of the fetal tissue. This has attracted considerable interest in recent years, but it is not yet fully understood. The adrenals at birth are large organs with a smooth, regular surface. Beneath the capsule a layer of cortical epithelium cells, the so-called permanent cortex, is present in which the zona glomerulosa and zona fasciculata can be distinguished. Inside, toward the medulla, the permanent cortex is lined by a mass of slightly larger [illegible]

[illegible] takes place in such a way that [illegible]

In 1927, M F Lucas Keene and E E Hewer wrote,

The possible function of those cells constituting the [illegible]

[illegible] fetal life puts great and very obvious difficulty in the way of any investigation of their physiological significance

Keene and Hewer point out that during the first year of life, the whole gland shrinks, owing to the rapid disappearance of the fetal cortex, the cells of which first become swollen and then lose their nuclei and are later replaced to a certain extent by temporary fibrous tissue, which forms a well marked zone central to the rapidly developing zona fasciculata Up to one year the central fibrous tissue is a marked feature,

The innermost layer of the cortex is formed by an anastomosing network of cells called the zona reticularis. These cells are about the same size as those of the second layer, but they contain little lipoid and show less vacuolation. Near the medullary border a number of cells contain abundant pigment in their cytoplasm and have, therefore, a brownish green color. These cells are called chromatophores.

The center of the adrenals is formed by a glandular core called the medulla. The cells of the medulla are not found throughout the whole space between the cortical envelope. In the periphery of the medullary core the cortical layers are separated by strands of connective tissue which contain rather large blood vessels. In the center the medulla has its greatest width and separates the cortical layers for a distance of several millimeters. In this "hilus," the medulla is composed of rounded groups or short cords of "basophilic" cells, which surround the large blood vessels and sinusoidal venules. These are the true medullary cells, derivatives of the ectoderm. If the cells are fixed in dichromate, fine brown granules may be found in them which show the "chromaffin" reaction. In addition, sympathetic ganglion cells are also present.

One peculiarity should be mentioned. The permanent cortex sometimes appears invaginated from the outside around the central vein. It is, therefore, common to find true cortex immediately around the central vessel within the medulla, an observation which is not pathologic, but which can easily lead to misinterpretation On the other hand, remnants of fetal cortex are also most likely found in the hilus area.

It is well known that medulla and cortex are derived from different embryologic tissues, and that both glandular tissues have a different function. The medulla is concerned with the production of adrenalin or a precursor of that substance. The endocrine function of the cortex has been discovered only in the last few decades. It is now known that the cortex plays an important role in glycogen and salt metabolism, and its activity is closely related to pituitary and gonadal function. Destruction of the cortex as seen in Addison's disease leads to a severe metabolic disorder; tumors of the cortex may have a striking virilizing effect in females. Pituitectomy leads to atrophy of the cortex, especially of the fasciculata and glomerulosa. Complete destruction of the cortex is not compatible with life.

Without going into the details of prenatal development, I should like to stress that one point must be remembered. The sympathicogenic tissue, which forms the medulla, immigrates from the outside into a pile of mesodermal cells, the central body (Cramer) or fetal cor-

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band of connective tissue which encapsulates the medulla at the end of the first year remains "as a vestige of the stroma of the fetal cortex." During the second year the band is obliterated and disappears. The permanent cortex increases in size, while the fetal cortex disappears, and it is now generally held that growth of the permanent cortex takes place from the glomerulosa. The vertical alignment of cells which represent the zona fasciculata appears during the second postnatal week, and the zona reticularis appears in the third postnatal month.

It is held that "the morphological types found in the adrenal cortex are different stages in the life history of the same cells" (Zwemer and coworkers). According to this view, which is now widely accepted, the cortical cells proliferate from the glomerulosa beneath the capsule, form the fasciculata, and finally the reticularis, in which the greatest amount of cell degeneration can be found.

If one summarizes the results of various studies made on animals and on the human adrenal, one may conclude: (1) that the fetal cortex disappears entirely after birth without leaving any trace, except under pathologic conditions, as a possible source of tumors (Grollman); (2) that the medulla is formed from neurogenic tissue entirely independent of the permanent cortex and the fetal cortex; and (3) that the permanent cortex is formed from mesothelium, independent of the fetal cortex. The permanent cortex grows from the outside toward the medulla, increasing rapidly after birth and continuing to grow up to an age of 17 to 20 years. The permanent cortex is the main and only source of the adrenocortical hormones.

This view seems fairly satisfactory and compatible with a number of observations made in children and in various animal species. It leaves, however, a gap in our knowledge, which is important enough to be emphasized, because a number of observations are not compatible with the view reported above. It may be mentioned that Cramer developed a slightly different opinion about the disappearance of the fetal cortex, or the "central body," as he termed it. In his opinion masses of connective tissue grow in tangential direction through the boundary zone, separating the tissue inside of the connective tissue from that on the outside. The cells between the connective tissue strands and the permanent cortex form a part of the reticularis, which would, therefore, be a different tissue from the other two layers of the permanent cortex. Most of the cells of the central body inside the boundary zone underg[illegible]
complet[illegible]

but it can no longer be discerned at three years of age. Although the border between permanent cortex and medulla is distinct, owing to the difference of tissue, the two components, cortex and medulla, are not separated by connective tissue strands. The normal medulla is not encapsulated. The permanent cortex increases in size, apparently from the periphery. The greatest amount of mitosis is found in the glomerulosa and in the outer fasciculata.

Although Keene and Hewer do not hold the view of Cramer that the "central body" participates in the formation of the medulla, these authors think that the true cortex, which persists postnatally, and the fetal cortex, which atrophies after birth, are not of common origin. This observation is based on different staining reactions. The cells of the fetal cortex are eosinophilic throughout their existence, whereas the cells of the true cortex are small basophil cells which never give an eosinophilic reaction. The study emphasizes the importance of the "central body" and its possible significance for pathology, but the authors do not offer any definite solution.

Keene and Hewer's view is confirmed by Unto U. Uotila, who has collected ample evidence that the permanent cortex is formed not from the fetal cortex, but from entirely new mesothelial elements proliferating from the celomic wall The permanent cortex differentiates gradually on the free surface of the fetal cortex and beneath the capsule. The later fate of the fetal cortex is thought to be complete degeneration, which starts during the last 10 weeks of intrauterine life and is completed by the end of the first year. Nothing is known concerning the function of the fetal cortex. It is formed before the permanent cortex and forms the bulk of the fetal adrenal. It persists as a well developed organ throughout intrauterine life, but it degenerates soon after birth. This suggests, according to Uotila, "that it serves some important function in the physiology of the embryo and fetus and is not a mere phylogenetic relic. The fetal cortex would seem to belong to that group of pre-natal structures which Streeter would regard as 'temporary devices,' with which some particular needs are met."

Details of the process of postnatal degeneration of the fetal cortex have recently been provided by Benner and Swinyard. The degeneration is in full swing at the end of the first postnatal week and is completed six to nine months after birth These authors hold the view that the connective tissue fibers do not separate the boundary zone from the permanent cortex, but are the original stroma which becomes "increasingly evident" as the cells disappear. They do not think that there is new formation of connective tissue, and the compact

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the central body undergo division and participate in the development of the medulla, which is formed "at the expense of the central body." He thinks that one has to look at the central body as the origin of or, at any rate, part of the medulla, and that the final medulla as a source of adrenalin is formed from the two tissues, the neurogenic and the fetal central body. According to Cramer, the medulla would reveal an arrangement similar to that seen in the pituitary, in which neurogenic and glandular tissues have united to form one endocrine system. Cramer reports a cretin in whom the formation of the medulla was inhibited, although the connective tissue reaction had commenced. Absence of the central body in hemicephaly has been reported by Elliott and Armour.

Although Cramer's view has not been accepted generally, there are some facts which are unexplainable by the theory that the reticularis is a part of the permanent cortex and develops from the outside layers Several investigators have associated the presence of the "adrenogenital syndrome" with a proliferation of the reticularis, which is considered by some as "androgenic tissue" Grollman especially has emphasized that this androgenic tissue is the source of virilizing influence in girls and may be the cause of abnormal sex differentiation in males and females. The discovery of a special zone, the juxtamedullary zone or x-zone, in certain animals, and its relation to sex development supports the view that the tissue between permanent cortex and medulla should be considered as a separate tissue with particular functions

The Adrenals in Mongolism

The observations made on 44 cases of mongolism are not only of interest with regard to the pathology of this condition, but at the same time throw some light on the problems discussed above The material can be divided into findings in infants and in children and adults

In contrast to the observations of Hirning and Farber in 1931—that the adrenal cortex showed a fairly normal appearance—a disorder of adrenal development was found in a high percentage of cases. In some, the fetal cortex was not involuted or, at least, considerable remnants were found several months after birth A second symptom was delayed involution, and remnants were seen throughout the first year

In the second group, that of children above 1 years and adults, pathology was consistent and striking in all cases

The permanent cortex remained at a level present after birth, and very little postnatal growth could be noticed. The fasciculata was



involution (C) 5 month old male Note high degree of nodulation (N) Permanent cortex (c) thin Involution (I) incomplete Medullary tissue (M) somewhat hypertrophic (D) 33 year old male Note hypoplastic degenerated permanent cortex (c) hypertrophic medulla (M) and reticularis (r)

narrow, the lipoid was sparse, and the cells and their arrangement were of infantile patterns In addition, considerable degeneration was present in a large number of cases In one case the cortex was destroyed, but no symptoms of Addison's disease had been observed.

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FIG 55—The adrenal in mongolism (H & E stain) (*A*) 4 year, 3 month old male (v, veins) Note thin permanent cortex (c) The medulla still consists of the persistent fetal cortex (f) without signs of involution (*B*) 4 month old male Note great amount of nodulation (N) of permanent cortex (c) Permanent cortex thin Persistent involution (I) with some medullary layers (M) within the zone of involution (*C*) 5 month old male Note high degree of nodulation (N) Permanent cortex (c) thin Involution (I) incomplete Medullary tissue (M) somewhat hypertrophic (*D*) 33 year old male Note hypoplastic degenerated permanent cortex (c), hypertrophic medulla (M), and reticularis (r)

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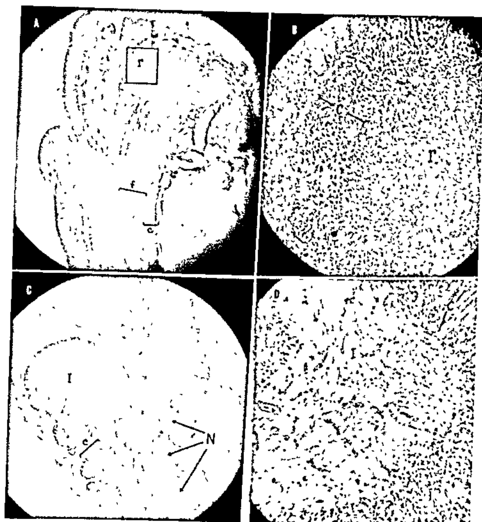


FIG 56 — The adrenal in mongolism (H & L stain) (*A*) 10 month old male Note unusual size of cortex (c) and especially persistent fetal cortex (f) There are no signs of involution (r, reticularis) (*B*) Same case, higher magnification (quadrant of *A*) Note thin permanent cortex (c) and hypertrophy of reticularis (r) as remnant of fetal cortex (*C*) 9 month old female Note abnormal nodulation (N), thin permanent cortex (c), large area of involution (I) (*D*) Same case, higher magnification. Note the meshy area of involution (I) without organization of parenchyma inside permanent cortex (c)

The medulla varied greatly in size True medullary cells were sparse in many cases, but a few showed hypertrophy A considerable amount of fibrosis was present with the hypertrophy The observations on the adrenal medulla permit the conclusion that medullary function is inadequate on account of insufficient development of the chromaffin cells

The most startling observations were made with regard to the

"boundary zone," or juxtamedullary zone. While the permanent cortex was hypoplastic and narrow, the zone between fasciculata and medulla was broad and outstanding The width of this zone was frequently equal to that of the combined two outer layers The cells of the boundary zone stained bright eosinophilic in the majority of observations There was a strong fibrous stroma, with bands of connective tissue, which encapsulated the medulla This "capsule" should normally disappear in the second year.

It is worthy of note that increased lobulation ("adenomata") is a common observation. The significance of such "adenomata" is still disputed It may, however, be mentioned that if the adrenals of mongoloid infants and children are compared with those of patients with cerebral palsy or other forms of mental deficiency, the increased lobulation in mongolism is conspicuous.

Another observation deserves mention, and that is the hypertrophy of the reticularis and the presence of large amounts of eosinophilic cells in the medulla

Whether these observations are indicative of abnormal involution or of a constant stress situation which is due to the congenital heart defect and other constitutional anomalies cannot yet be decided.

THE LIVER

The liver of the mongoloid has not been described by other investigators. Brousseau did not mention any liver pathology in his monograph on mongolism (1928).

The liver was studied in 52 cases, and 43 of the observations are reported in table 10 Four features are found with some regularity: fatty vacuolization, fibrosis, degeneration of the parenchyma and congestion The enumeration of the causes of death adds further evidence that the fatty changes in the liver are not correlated with chronic infections

Fatty Vacuolization

This descriptive term is used rather than the term "fatty infiltration" or "fatty degeneration" because it has, at the present time, not been demonstrated whether the fat in the livers is "storage fat" or not In many cases there is no indication that the cells that carry the fat are otherwise injured On the other hand, the cells often show obvious degeneration, but neither of these findings is conclusive proof of the nature of the fat droplets, and only physiologic and histochemical methods can definitely settle the point. Therefore, the noncommittal term "fatty vacuolization" is used. In 12 mongoloids from 9 days to



Fig. 56.—The adrenal in mongolism (H & E stain). (*A*) 10 month old male. Note unusual size of cortex (c) and especially persistent fetal cortex (f). There are no signs of involution (r, reticularis). (*B*) Same case, higher magnification (quadrant of *A*). Note thin permanent cortex (c) and hypertrophy of reticularis (r) as remnant of fetal cortex. (*C*) 9 month old female. Note abnormal nodulation (N), thin permanent cortex (c), large area of involution (I). (*D*) Same case, higher magnification. Note the meshy area of involution (I) without organization of parenchyma inside permanent cortex (c).

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The initial stages of fatty vacuolization sometimes show a distribution along the central veins, but this is not at all a general rule, and the fat is actually more often and to greater extent found around the portal vessels Two cases were seen in which the fat was accumulated along the central as well as the portal vessels, leaving only the intermediary zones of the lobules relatively free from fat In the most advanced stages (4 of 31, or about 13 per cent), all liver cells contained at least one big droplet of fat which filled almost the whole cell and compressed the nucleus. These livers actually simulate fat tissue (fig. 57*B*). The fat droplets reach the size of 50 μ, yet in all these cases of most severe fatty vacuolization it is possible to trace the original pattern of the lobule, the liver cords being only slightly and mechanically displaced Furthermore, there is a considerable amount of cytoplasm in the spaces between the droplets which appears essentially normal.

Macroscopically, the livers are rarely of the extreme fatty type, even when 50 per cent and more of the cells are seen microscopically to contain large fat droplets On sections, only one liver was found to be actually oozing fat, and this liver was also the only one that floated on water (case 148). The great majority of the livers show a yellowish tinge In those cases in which the fat is diagnosed at autopsy, one is surprised at microscopic examination to see the great amount which is actually present in the cells

Fibrosis

Fibrosis is not as constant a finding as is the fatty deposit. It occurs, however, in more than 50 per cent of the older age group Typically, it does not present the picture of a liver cirrhosis True nodular cirrhosis was not found at all in the 43 cases of this study The great majority of those cases which show a conspicuous increase in fibrous tissue have a pronounced periportal proliferation and also a thickened capsule, but the intertrabecular spaces show little or no increase in connective tissue The liver cords, therefore, are not compressed or replaced Macroscopically, there are sometimes ...

... is not diagnosed at autopsy.

Case 125 and case 65 show fully developed liver cirrhosis, but even here the great amount of fibers is not present in solid masses and does not lead to a conspicuous hardening of the liver or to the formation of nodules. In the foreground is a severe necrosis of the parenchyma with no signs of regenerative foci. Case 65 clearly shows a considerable amount of fatty vacuoles, but none were found in case 125 This case is that of the only Negro mongoloid in the series The

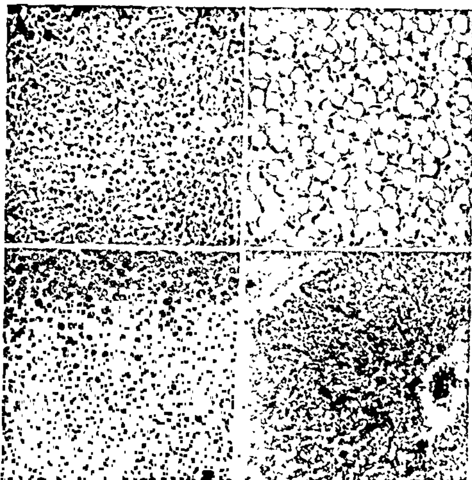
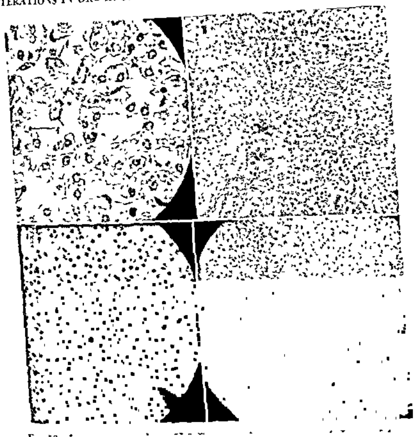


FIG. 57.—(*A, top left*) Liver congestion in a 2½ month old mongoloid baby (G-181). Liver shows a high degree of congestion with severe compression of the liver cords. Fat is rare, but a few fatty vacuoles are visible in the picture. H & E stain, *magnification 270 times. (B, bottom left) Fatty vacuolation in the liver of a 16 year* old mongoloid girl (11/118). The cytoplasm is much compressed by the big fat [illegible] tion in a 16 year old mongoloid (10/58). Congestion (black in picture) is severe around the lobular centers, fat is accumulated near the portal vessels. Masson stain, magnification 180 times.

1 year 10 months old, an abnormal amount of fat (++) occurred in 2 cases, or about 17 per cent. Of 31 cases above 2 years 4 months old, 25 (about 80 per cent) carried a *definitely abnormal amount of fat* (++ to ++++). Other pathologic characteristics are probably secondary to the fatty changes, except for the cases of severe congestion in infancy.



[...]uoles have been identified as neutral fat by specific fat stains (Sudan IV). In one recent case (that of a 38 year old male) all liver cell cytoplasm was replaced by large fat droplets. At the same time, the 38 year old male showed extensive senile plaques in the brain.

many cases, by a definite but limited periportal fibrosis. A comparison with a group of 50 feeble-minded, nonmongoloid patients of the same age group showed that fatty infiltration of the liver occurred half as frequently as in mongoloids, and again the incidence was about the same in nontuberculous and in tuberculous patients. Tuberculois, therefore, can only play an unimportant role in the etiology of the fatty livers.

liver is atypical of mongolism. (Further doubt is thrown on the diagnosis through the fact that the thyroid and pituitary glands were also not typical. The diagnosis was based on the presence of many external stigmata, such as the formation of the skull, hypotonia and rudimentary epicanthal folds.)

In addition to these two cases of liver cirrhosis, one of which is not definitely established as a mongoloid, there are two other cases which might be called "cirrhosis in its initial stages" The majority of cases show a limited but definite periportal fibrosis, which appears to have little tendency to proliferate further at the expense of liver tissue.

Congestion

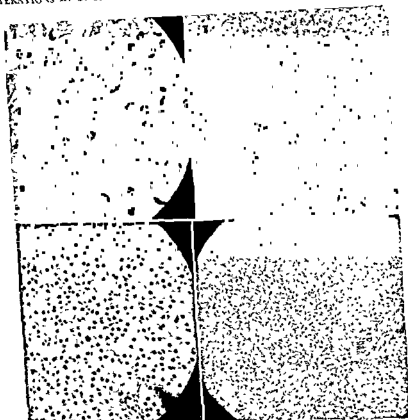
Two-thirds of the cases below 2 years of age showed congestion, and in a few below 1 year of age this feature dominated the whole picture (fig. 58). In the extreme cases (94, 181, 15) there was not only a uniform engorgement of all the sinusoids, but there were hemorrhagic necroses around the central veins The trabeculae were thinned and compressed and the liver appeared severely injured, as a whole. This high degree of congestion was rarely found in the older cases It is hardly remarkable that about 45 per cent of these should show congestion of varying degrees, as the terminal diseases and the circulatory failure at death might easily produce this picture In almost all the cases, the congestion is confined to those areas which do not show extreme fatty vacuolization However, the opposite distribution was observed in two cases.

Degeneration

It appears of some significance that severe cell degeneration is so rarely found in mongoloid livers. Necrotic foci and limited areas in which the liver cells appear damaged are frequent, and this is not surprising, in view of the fact that so many of the livers show tuberculosis and signs of terminal infections. Severe generalized degeneration and necrosis were found in only four livers, two of which were tubercular.

As a supplement to the account given above, it is interesting to mention the case of a 17 year old mongoloid boy (case 90) who was clinically regarded as a borderline case. He was of normal body length, 159 cm. His brain weight was the only normal one in the whole series. His gonads were developed better than usual in a mongoloid. His liver turned out to be the only completely normal one seen in 31 livers of mongoloids of over 2 years of age.

The liver of the mongoloid of 2 years or older is a fairly well defined pathologic entity, with its large amounts of fat accompanied, in



Liver of 5 month mongoloid female Note severe fatty infiltration (*D*) Liver of 33 year old mongoloid female Note very severe fatty degeneration of liver cells, the large vacuolization in practically every cell, with loss of liver cytoplasm The vacuoles have been identified as neutral fat by specific fat stains (Sudan IV) In one recent case (that of a 38 year old male) all liver cell cytoplasm was replaced by large fat droplets At the same time, the 38 year old male showed extensive senile plaques in the brain

many cases, by a definite but limited periportal fibrosis A comparison with a group of 50 feeble-minded, nonmongoloid patients of the same age group showed that fatty infiltration of the liver occurred half as frequently as in mongoloids, and again the incidence was about the same in nontuberculous and in tuberculous patients. Tuberculois, therefore, can only play an unimportant role in the etiology of the fatty livers

One of the outstanding factors in the pathology of the liver of mongoloids is the complete change in the picture at the age of 1½ to 2 years. *Figure 59 adds* significance to this observation by comparing the ponderal index of the mongoloid with that of the normal. The ponderal index—that is, the relative weight—is below normal up to the age of about 1½ years. It is very nearly normal from 1½ to 3 years, and from then on for the rest of the mongoloid's life it remains at a high level above normal. It is hardly a coincidence that the liver fat begins to appear with great regularity at the same time when the mongoloid becomes generally obese. The reason for this obesity is, in all probability, the deficiency in thyroid and pituitary secretions. The endocrinologic section of this book presents ample confirmation of this view.

The mongoloid baby is usually underweight and its endocrine balance is obviously different, the difference being reflected in the

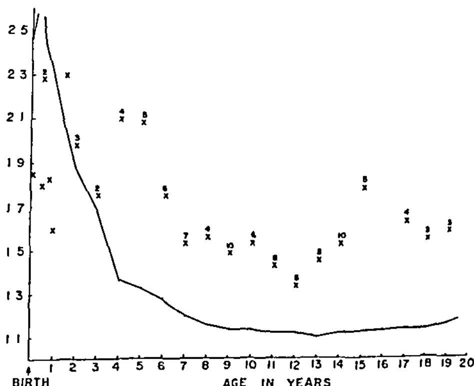


Fig. 59.—Ponderal index (weight divided by 100 times the cube of body length) The unbroken line represents the normal values designed for citizens of the United States (Engelbach, 1932) The crosses represent values found in mongoloid patients. The numbers indicate the number of cases of which the value represents an average Crosses without numbers represent individual cases The picture indicates clearly that in the first two years of life the ponderal index of mongoloid babies is far below normal while after two years all values are far above

liver. Many of the livers at this age are normal, but an extraordinary amount of congestion is found often enough to regard it as a typical feature. It has been demonstrated that the abnormalities and deficiencies of the adrenals in the mongoloid infant bring about many of the characteristic features in its development. It has also been shown (Conwin) that dogs which are deprived of their adrenals show great vascular congestion and hemorrhages around the central veins in the livers. It appears justified, therefore, to speculate on the possibility that the pathology of the liver of the mongoloid infant is correlated with a suprarenal insufficiency. The fact is remarkable that all the severely congested livers below 2 years of age were very much underweight. About one-third of the livers below 2 years of age were found to be normal.

The weights of the livers are shown in table 10. Of 34 cases, 20 were underweight, 8 within normal range and 6 overweight (see normal values of Coppoletta and Wolbach, 1933). When it is considered that mongoloids are also below normal in height, the low values appear less remarkable. A few livers, as in cases 94, 181, 139, 58, et cetera, are [illegible]

[illegible] is only about 75 per cent of the normal. Little explanation [illegible]

[illegible] o a decreased [illegible] The material [illegible]

[illegible] in themselves. In the first place [illegible]

[illegible] the liver, and cortical insufficiency decreases the storage. There are reasons to suppose that such an insufficiency may play a direct part in the deficient glycogen storage of the liver in mongolism.

HEART AND VASCULAR SYSTEM

Anomalies of the heart and vascular tree are most common in mongolism. More than 60 per cent of our patients reveal a heart murmur and evidence of septum defect. Although in the remaining cases no septum defect or patent foramen ovale can be demonstrated

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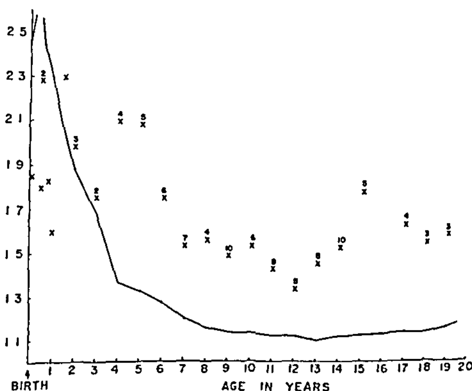


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The weights of the livers are shown in table 10. Of 34 cases, 20 were underweight, 8 within normal range and 6 overweight (see normal values of Coppoletta [illegible]

very much underweight. In case 139, for instance, there was very fatty liver without signs of degeneration of the liver cells, and yet the weight of the liver is only about 75 per cent of the normal Little explanation can be found for this, but the suggestion is made that the small livers are part of the picture of splanchnomicria described elsewhere

The liver function of the mongoloid child is not greatly impaired clinically However, there is a definitely increased glucose tolerance, and the insulin tolerance curves indicate a tendency to a decreased ability to raise the blood sugar level (Bixby and Benda). The material fixed for glycogen preservation, although not conclusive at present, tends to confirm the view that the mongoloid liver is deficient in glycogen Several possibilities which together or singly may bring about this deficiency suggest themselves. In the first place, while fatty deposits do not preclude the storage of glycogen, extreme fat accumulation appears to suppress it markedly Second, the adrenal cortex governs the glycogen storage in the liver, and cortical insufficiency decreases the storage There are reasons to suppose that such an insufficiency may play a direct part in the deficient glycogen storage of the liver in mongolism

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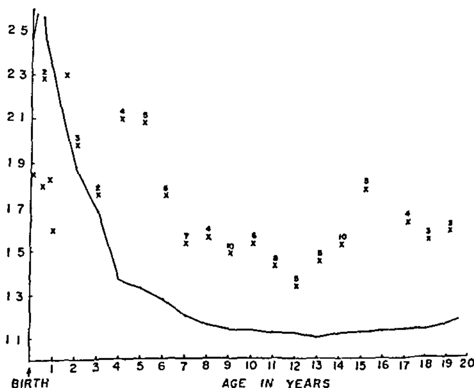


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116	F	15 4/12	1100	+	–	–	++	–	Tb miliary
109	F	15 8/12	1135	+++	++	++	++	+	Tb of lungs
148	M	15 10/12	1650	++++	+	–	–	+	Tb of lungs
85	M	16	1400	+++	+++	++	++	–	Status epilepticus
59	M	16 3/12	850	+++	++	++	–	+	Tb of lungs
91	M	17	1140	++++	++	–	–	+	Tb of lungs
90	M	17	1590	–	–	–	–	–	Gangrene of lung
126	F	17 1/12	1050	+++	+++	–	+	–	Tb of lungs
83	M	17 9/12	880	+++	+	++++	–	+	Tb of lungs
65	M	18 1/12	2100	++	++++	+	++	–	Tb of lungs
146	M	18 4/12	1510	++	++	–	+++	–	Tb of lungs
M 3	F	20	?	+	+++	++	+++	+	Tb
22	M	20 6/12	?	+++	++	++	++	–	Bronchopneumonia
71	F	28 3/12	820	++	++	++	–	+	Tb of lungs

\+ slight degree, pathology questionable

++ certainly pathologic in amount, but not very pronounced

+++. marked degree.

++++: extreme degree throughout organ

The presence of tubercular foci is marked with a cross regardless of the degree of involvement

TABLE 10.—*Condensed Chart of the Findings in the Livers of Mongoloids*

Case no.	Sex	Age	Weight (Gm.)	Fat	Fibrosis	Congestion	Cell degen.	Liver Tb.	Cause of death
C 76	F	9 days	90	–	–	++	–	–	?
C 91	F	6 wks.	76	–	–	++++	++	–	?
C 162	M	2 mos.	?	–	–	+	–	–	?
C 181	M	2½ "	75	–	–	+++	–	–	?
C 95	M	3½ "	?	+	+	–	–	–	?
C 62	F	6 "	260	++	++	++	–	–	?
120	M	7 "	240	+	+	++	+	–	Lobar pneumonia
15	M	7½ "	160	–	–	+++	–	–	Multiple abscesses
152	M	8 "	190	+	–	++	–	–	Scarlet fever
151	M	1 6/12	295	+	+	–	–	–	Meningitis
130	M	1 8/12	?	++	++	++	++	–	Bronchopneumonia
102	M	1 10/12	390	–	–	–	–	+	Tb., Meningitis
C 102	F	2 3/12	?	+++	++	+	++	–	?
99	M	4 5/12	570	++++	+	–	–	–	Brain edema
57	F	4 5/12	150	+++	++	–	++	–	Septic sinus thrombosis
103	M	6 7/12	680	++	++	+++	+++	–	Lung abscess
124	M	7	640	+++	+++	–	–	–	Lung embolism
118	M	7 8/12	605	++	–	++	++	+	Tb. of lungs
17	F	8 7/12	800	+	++	+	+	–	Diphtheria, pneumonia
25	M	8 8/12	?	++	+	–	–	–	Bronchopneumonia
125	M	8 9/12	670	–	++	+++	++++	+	Tb. of lungs
131	F	9 7/12	710	+	+	+	–	–	Intussusception
17	F	9 8/12	160	+++	++	+++	+++	–	Bronchopneumonia
141	M	10 4/12	740	++++	+	–	–	+	Tb. of lungs
139	M	11 3/12	690	+++	++	+	–	–	Bronchopneumonia
133	F	12	?	++	++	++	–	–	Volvulus
82	F	13 10/12	890	+++		–	–	+	Tb. of lungs
155	M	14 4/12	?	++	–	–	++	+	Tb. of lungs
32	M	14 11/12	830	+++	+	–	–	–	Bronchopneumonia

116	F	$15^{4}/_{12}$	1100	+	–	–	++	–	Tb, miliary
100	F	$15^{8}/_{12}$	1135	+++	++	++	++	+	Tb of lungs
148	M	$15^{10}/_{12}$	1650	++++	+	–	–	+	Tb of lungs
85	M	16	1400	+++	+++	++	++	–	Status epilepticus
58	M	$16^{3}/_{12}$	850	+++	++	++	–	+	Tb of lungs
81	M	17	1140	++++	++	–	–	+	Tb of lungs
90	M	17	1590	–	–	–	–	–	Gangrene of lung
126	F	$17^{1}/_{12}$	1050	+++	+++	–	+	–	Tb of lungs
83	M	$17^{9}/_{12}$	850	+++	+	++++	–	+	Tb of lungs
65	M	$18^{1}/_{12}$	2100	++	++++	+	++	–	Tb of lungs
146	M	$18^{4}/_{12}$	1510	++	++	–	+++	–	Tb of lungs
M 3	F	20	?	+	+++	++	+++	+	Tb
22	M	$20^{6}/_{12}$	?	+++	++	++	++	–	Bronchopneumonia
71	F	$28^{5}/_{12}$	820	++	++	++	–	+	Tb of lungs

+ slight degree, pathology questionable
++ certainly pathologic in amount, but not very pronounced
+++: marked degree
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C 162	M	2 mos	?	−	−	+	−	−	?
C 181	M	2½ "	75	−	−	+++	−	−	?
C 95	M	4½ "	?	+	+	−	−	−	?
C 62	F	6 "	260	++	++	++	−	−	?
120	M	7 "	240	+	+	++	+	−	Lobar pneumonia
15	M	7½ "	160	−	−	+++	−	−	Multiple abscesses
152	M	8 "	190	+	−	++	−	−	Scarlet fever
154	M	1 6/12	295	+	+	−	−	−	Meningitis
140	M	1 8/12	?	++	++	++	++	−	Bronchopneumonia
102	M	1 10/12	390	−	−	−	−	+	Tb, Meningitis
C 102	F	2 5/12	?	+++	++	+	++	−	?
99	M	4 5/12	570	++++	+	−	−	−	Brain edema
57	F	4 5/12	450	+++	++	−	++	−	Septic sinus thrombosis
103	M	6 7/12	680	++	++	+++	+++	−	Lung abscess
124	M	7	640	+++	+++	−	−	−	Lung embolism
118	M	7 8/12	605	++	−	++	++	+	Tb of lungs
47	F	8 7/12	800	+	++	+	+	−	Diphtheria, pneumonia
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155	M	14 4/12	?	++	−	−	++	+	Tb of lungs
32	M	14 11/12	830	+++	+	−	−	−	Bronchopneumonia



FIG. 60.—[illegible]
contrast to [illegible]
Note the un[illegible]
which thymus tissue is present. (A) Thymus of 5 month mongoloid female. (B) Thymus of 10 month mongoloid male. (C) Thymus of 9 month mongoloid female. (D) Thymus of 2 year, 8 month mongoloid female. (E) Thymus of 4 year mongoloid female. (F) Thymus of 5 year, 3 month mongoloid male.

alies of the heart and underdevelopment of the vascular tree are regular features.

It has been pointed out in chapter II that the heart frequently shows congenital defects. Their number is so great that the heart is found abnormal in 75 per cent of the infants who die in the first two years of life. In those who survive, a large percentage shows congenital heart malformations. The intra-auricular septum shows an open foramen ovale in the majority of cases. If the defect is restricted to a small hole which admits the passage of a probe only, it is of no clinical significance. The presence of a real defect in the septum, however, is not rare. Such a defect may be even more conspicuous in the intraventricular septum, in which some openings measured as much as 1 inch in diameter. Abnormalities of the arteries, Fallot's tetralogy, patent ductus Botalli and dextrocardia may be found. Little attention has been paid to the anomalies of the cusps of the mitral and tricuspid valves. The cusps are uneven, short, and the edges nodular. Fetal endocarditis seems suggested, but there is little evidence otherwise, and it appears more likely that these nodules are the nodules of Albini, which are embryonic remnants. This is another confirmation of the general fetalism of the mongoloid child.

The vascular system as such is hypoplastic. All arteries remain narrow, thin, and the vascular tree shows fewer branches than occur in normal controls. This is conspicuous in the brain. The capillaries appear congested and enlarged. Hemangiomata in the kidneys, liver and other organs are not rare Two children had periarteritis nodosa; one died with the symptoms of intestinal intussusception with generalized periarteritis The other child had periarteritis in the testes and in a few other organs In mongoloids beyond 25 years of age, atheromatosis of the arteries is common.

LUNGS

It is difficult to say whether or not the lungs in mongolism show certain peculiarities which are characteristic of this condition. Radiologists who have to deal with mongoloid patients consider a diagnosis particularly difficult. It is certain that the respiratory mucosa is extremely vulnerable and susceptible to infections. In previous decades, mongoloid children showed a great susceptibility to tuberculosis; but with modern preventive measures, tuberculosis in mongoloid children and adults has become rare in our material. However, pneumonias are not rare and pneumonitis as a chronic condition often develops.

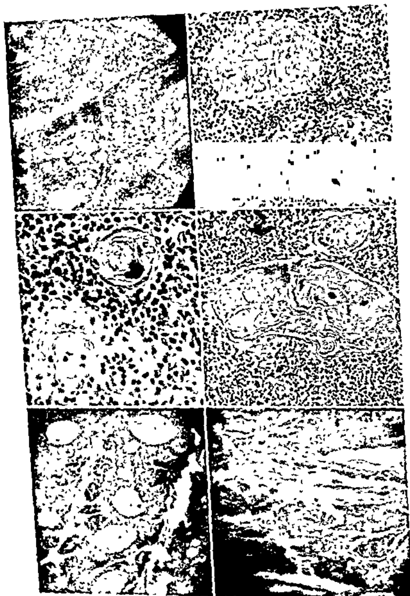


FIG. 60 – Thymus in mongolism (H & E stain). The thymus is relatively large in [illegible] month mongoloid male. (C) Thymus of 9 month mongoloid female. (D) Thymus of 2 year, 8 month mongoloid female. (E) Thymus of 4 year mongoloid female. (F) Thymus of 5 year, 3 month mongoloid male.

THE THYMUS

The pathology of the thymus is in general still not well established, with the exception of the particular features seen in some cases of myotonia. Our observations in mongolism indicate that there are often rather large masses of thymus tissue to be found in the sternal notch and on the pericardium. Conspicuous are huge Hassall bodies, of a size which I have not seen in any of the control material. The significance of these observations is not known.

INTESTINAL ORGANS

Two abnormal features may be observed in the intestines. Microcolon is not rare, on the one hand, by extreme extension of parts of the colon, and a true macrocolon may also be observed. Constipation is frequent in mongoloids but usually reacts well to small dosages of thyroid unless stasis of a macrocolon cannot be overcome.

KIDNEYS

The kidneys show certain characteristic features which have so far *escaped recognition. They are small and underweight.* This becomes more conspicuous in the second half of the first decade, when renal infantilism seems at its height. Development of the glomeruli is slow and they remain near the capsule in a distribution characteristic of fetal and early postnatal life. Interstitial fibrosis, however, seems rare, and one may state that the organs of mongoloid patients seem generally weak in interstitial response on the part of the connective tissue. Loose hemangiomata were found in several cases.

CHAPTER VIII

HEMATOLOGY AND BIOCHEMISTRY

HEMATOLOGY*

Blood Groups

In each racial group a characteristic distribution of the four blood types exists. Among Caucasians the distribution is distinctly different from that found in people of the Mongolian race. The reports of a study of American mongoloids indicate that the percentage distribution of blood types was the same as that reported for a total of 10,556 unselected Americans.

According to Bernstein's formula, which is based on his triple allelomorph theory, the frequencies of the agglutinogens A and B among our mongoloid defectives agree closely with those calculated for average Americans. These frequencies also agree with those found by Penrose in his studies of English mongoloid patients. Table II includes combined totals for the English and American mongoloids as well as figures for Japanese and Chinese, calculated from Strandskov's data, for comparison.

Since the frequency of agglutinogen B is relatively high in the Mongolian race and low in American and European populations, the data support Penrose's position in opposing the hypothesis, suggested by Down and Crookshank, that mongoloid deficiency is due to racial regression.

Blood Counts

The following is a summary of the observations we have made during our years of research and clinical experience with mongoloids.

Number of Erythrocytes, Including Reticulocytes

Although the general trend is low, the majority of cases are within the normal range (4,000,000 to 5,000,000 red cells). In all age groups,

* Some of the data presented in this chapter have been collected in collaboration with Dr. E. M. Bixby at Wrentham State School (see [illegible] named). The other [illegible]
the Fernald School [illegible]
and Mr. Martin B. [illegible]

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The pathology of the thymus is in general still not well established, with the exception of the particular features seen in some cases of myotonia. Our observations in mongolism indicate that there are often rather large masses of thymus tissue to be found in the sternal notch and on the pericardium. Conspicuous are huge Hassall bodies, of a size which I have not seen in any of the control material. The significance of these observations is not known.

INTESTINAL ORGANS

Two abnormal features may be observed in the intestines. Microcolon is not rare, on the one hand, by extreme extension of parts of the colon, and a true macrocolon may also be observed. Constipation is frequent in mongoloids but usually reacts well to small dosages of thyroid unless stasis of a macrocolon cannot be overcome.

KIDNEYS

The kidneys show certain characteristic features which have so far *escaped recognition They are small and underweight.* This becomes more conspicuous in the second half of the first decade, when renal infantilism seems at its height. Development of the glomeruli is slow and *they remain near the capsule in a distribution characteristic of* fetal and early postnatal life. Interstitial fibrosis, however, seems rare, and one may state that the organs of mongoloid patients seem generally weak in interstitial response on the part of the connective tissue. Loose hemangiomata were found in several cases.

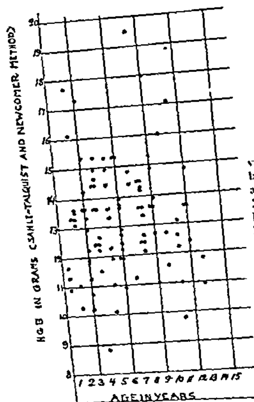


FIG 61—(A) Hemoglobin values in Gm. per 100 ml blood according to Talquist and Newcomber methods Note that few subjects have low values the majority have high average and even above average levels

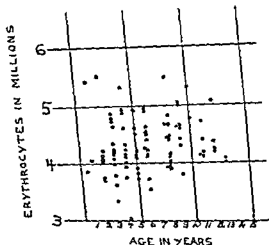


FIG 61—(B) Erythrocyte counts in mongolism. The majority of patients hav counts between 4 and 5 million, with several counts between 5 and 6 million. Sev eral cases of moderate anemia with counts below 4 million

TABLE 11.—*Distribution of Blood Groups*

Subjects	Total	Number in blood group*				Percentage in blood group*				Frequencies of agglutinogens	
		I AB	II A	III B	IV O	I AB	II A	III B	IV O	A	B
Americans (Strandskov)	10,536	477	4,121	1,208	4,730	4.5	39.1	11.5	44.9	24.9	8.3
Persons with mongolism, American	125	5	48	12	60	4.0	38.4	9.6	48.0	24.1	7.1
Persons with mongolism, English (Penrose)	166	3	83	14	66	1.8	50.0	8.4	39.8	30.6	5.2
Persons with mongolism, American and English	291	8	131	26	126	2.8	45.0	8.9	43.3	27.8	6.0
Japanese (Strandskov)	12,327	1,120	4,655	2,599	3,953	9.1	37.8	21.1	32.0	16.5	27.1
Chinese (Strandskov)	2,500	249	823	652	776	10.0	32.9	26.1	31.0	24.4	20.1

* Roman numerals indicate Moss groups and letters Landsteiner groups

about a quarter of the cases have counts below 4,000,000, but only a few show values as low as 3,000,000.

The reticulocyte count ranges between 0.3 per cent and 1.9 per cent, these values being definitely far below what is generally considered average (1.5 per cent).

Hemoglobin

The hemoglobin values spread over a large range. Although a few cases will show low values, a considerable number have high ones. In general, the distribution of the values is approximately the same for all age groups, but the occurrence of somewhat lower values in children from one to four should not cause alarm.

Cell Volume

The cell volume values fall within the normal range of 31 to 41 per cent. However, the average for children of 1 to 4 years (36.2) is slightly below the normal average of 38.86, and in older children (4 to 15 years), the average of 36.9 is again below the normal average (38.52).

Sedimentation Rate

In the majority of cases, the sedimentation rate is within the normal range (7 to 14 mm./hr.).

Fragility Test

Although there is some disagreement about what should be considered normal, for the most part, values coincide with Osgood's range. All complete hemolysis values are in the normal range

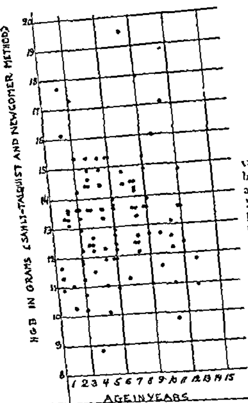


FIG 61—(A) Hemoglobin values in Gm per 100 ml. blood according to Talquist and Newcomber methods Note that few subjects have low values; the majority have high average and even above average levels.

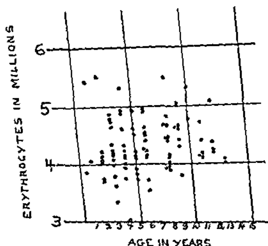


FIG 61—(B) Erythrocyte counts in mongolism The majority of patients have counts between 4 and 5 million, with several counts between 5 and 6 million. Several cases of moderate anemia with counts below 4 million

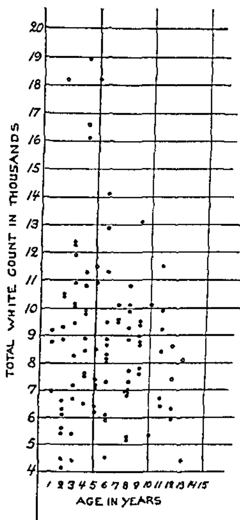


FIG 62—Total white cell count in thousands.

Total Leukocyte Counts

On the whole, in all age groups the cases are rather evenly distributed over the normal range (6000 to 11,000).

The Percentage Differential

Differential counts of the polymorphonuclear cells show an equal percentage distribution from the first to the tenth year of age, whereas in the age group of 10 and older, the average white cell count is lower.

The lymphocytes found in previous studies run below average (normal ±30 per cent), the results falling in the lower 20's in the majority of cases. However, our recent studies show that the percentage of lym

phocytes seems definitely increased in relation to polymorphic nucleated cells, and percentages of 60 per cent and more are not rare.

The percentages of eosinophils are low. Approximately two-thirds of all cases have less than 3 per cent, and many have no eosinophils at all Only occasionally are higher percentages noted.

The average monocyte count is low in the one to four year old group, with few exceptions. The average is slightly higher in the four to 14 year old group, the majority of the cases falling within the 4 to 8 per cent range. The basophils are normal. There seems to be a slight increase in disintegrating cells, although these are within range in most cases.

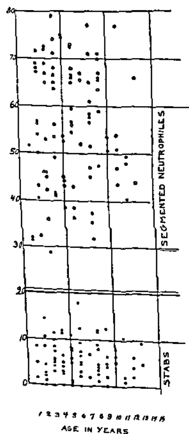


Fig 63

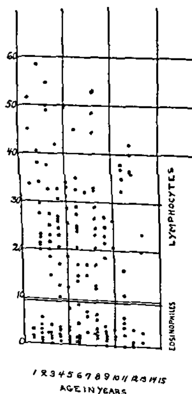


Fig 64

Fig 63 – Differential white cell counts stabs and segmented neutrophils
Fig 64 – Differential white cell counts eosinophils and lymphocytes, in per cent

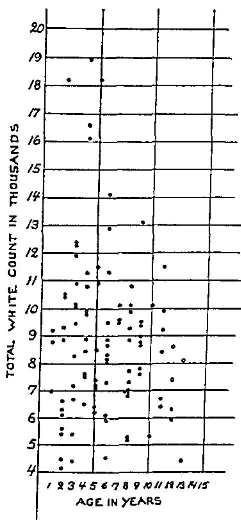


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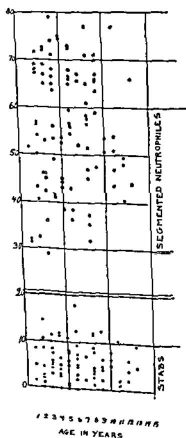


Fig. 63

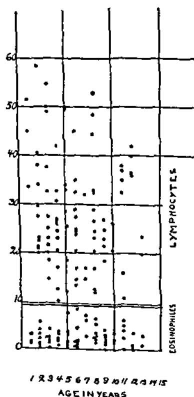


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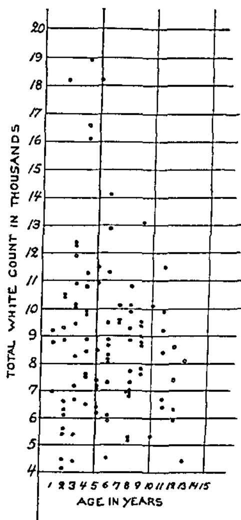


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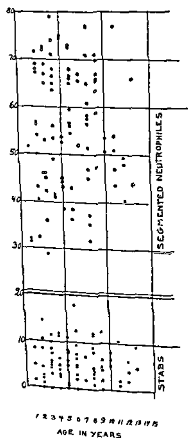


Fig 63

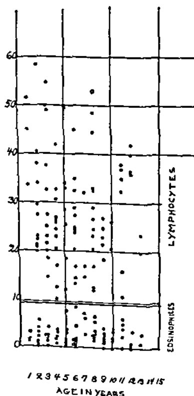


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Fig 64 — Differential white cell counts eosinophils and lymphocytes, in per cent

Absolute Differential

Although absolute counts of each type of leukocyte are seldom presented, it is important to determine whether there is a general tendency towards underactivity rather than overactivity of certain hematopoietic systems. Despite the wide range in absolute counts, they stay below 7,000 with few exceptions. A number of counts of seg-

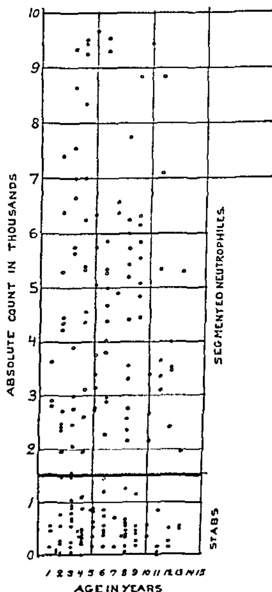


FIG. 65.—Absolute white cell counts in mongolism: stabs and segmented neutrophils.

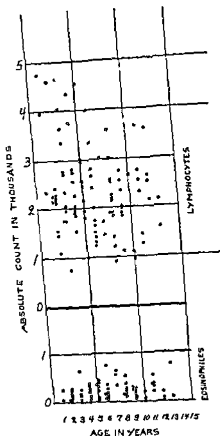


Fig 66—Absolute white cell counts in mongolism: eosinophils and lymphocytes

mented polymorphonuclear cells fall below 3000. The vast majority of lymphocyte counts are less than 3000 The majority of the monocyte counts range between 100 and 750.

Blood studies of patients with mongolism have been further conducted by Shapiro (1949), Lüers and Luers (1954) and Mittwoch (1957 and 1958). These studies confirm the observation reported above—that the polymorphonuclear leukocytes show an increased proportion of cells with unsegmented nuclei—thus providing further evidence of a shift to the left of the Arneth index. Torre, Scarzella and Zanalda also confirm this.

An aspect of extreme interest was added to the blood studies when, in 1954, Davidson and Robertson Smith found that a proportion of

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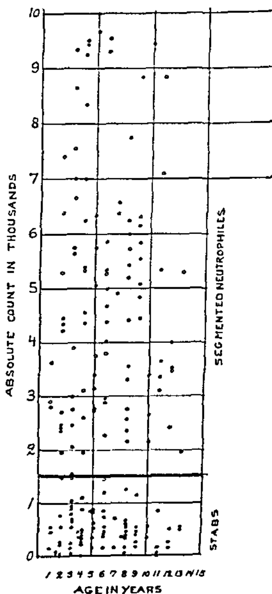


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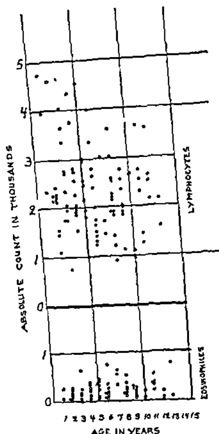


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An aspect of extreme interest was added to the blood studies when, in 1954, Davidson and Robertson Smith found that a proportion of

the polymorphonuclear neutrophil leukocytes of females carry a solitary nuclear appendage which is called a "drumstick." It is generally assumed that among 500 neutrophils, as many as 14 drumstick cells may be encountered. In Mittwoch's study, drumstick cells were encountered in the female mongoloids with a mean incidence of 3.8 per 500, which indicates a significant lowering from the norm. Drumsticks were not found in any of the male mongoloids reported in Mittwoch's study. In conclusion, she reported that an examination of 36 blood films from mongoloid children showed that the nuclei of the polymorphonuclear neutrophil leukocytes were less segmented than those of a similar group of nonmongoloid children. The incidence of the drumstick appendage in the neutrophil leukocytes of females was lower in the mongoloids than in the controls. In her study, the total leukocyte counts of 24 mongoloids and 24 controls showed no significant difference. In the mongoloids, the percentage neutrophil count was higher, and the absolute and percentage lymphocyte counts were lower than in the controls.

In a second article (1958) about the leukocytes in mongolism, Mittwoch concluded that the neutrophil count of the mongoloids was significantly higher than that of the controls The mean count for mongoloids was 5,184 and that for the controls, 4,018. The lymphocyte count of the mongoloids was significantly lower than that of the controls. The mean count for the mongoloids was 2102 and that for controls, 2888 The lymphocyte count in the controls fell with increasing age, while that of the mongoloids remained stationary. She mentions that the most striking difference between the mongoloids and controls in the present series was the low lymphocyte count in the mongoloids belonging to the younger age group, i.e., between three and six years. This low lymphocyte count was associated with a rather high neutrophil count. Normally, infants have a high lymphocyte count, which gradually falls with age At the age of four years, lymphocytes and neutrophils should be present in about equal numbers of, roughly, 4000 per cubic millimeter. Thereafter, the lymphocyte count continues to fall throughout childhood.

Mittwoch goes on to say that in the older age group, the differences between the mongoloids and controls have become smaller This is largely due to the fact that the fall of the lymphocyte count with age, which is found in normal children and which was observed in the mentally defective controls, did not occur in the mongoloids whose lymphocyte count was low throughout the whole age group investigated It seems more likely that a qualitative difference is involved. Since mongolism predisposes to leukemia, it is felt that the cause of

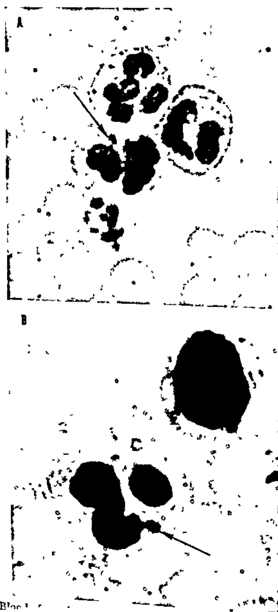


FIG 67 —Bl[illegible]
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segmented bl[illegible]

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FIG. 69.—Blood of female mongoloid, 14 months of age (Wright stain, oil immersion). Note primitive, undifferentiated patterns of segmented cells with vacuolization of cytoplasm and nucleus

veal a severe cellular inadequacy of hematopoiesis As figures 67 and 68 demonstrate, the segmentation of blood cells in mongoloid pa-

pear of the same nature Further investigations will decide the significance of these observations Figure 69 shows another aspect which

reported by Krivit and Good in America and by a group of research workers from the Western General Hospital, Edinburgh, Scotland. Krivit and Good summarize their observations by saying:

> A nationwide survey revealed that in the years 1952–1955, inclusive, a minimum of 31 cases of simultaneous leukemia and mongolism occurred in the United States in the 0- to 4 year age group. The maximum number of



FIG. 68—Blood of two male mongoloids (Wright stain, oil immersion) showing the female "drumstick" patterns in segmented cells (*A*) 10 year old, (*B*) 11 year old (*See text*, page 161)

the abnormal leukocyte counts in children with mongolism is worth investigating.

While our own observations agree in general with the findings reported by Mittwoch, observations on the blood cells in mongolism re-

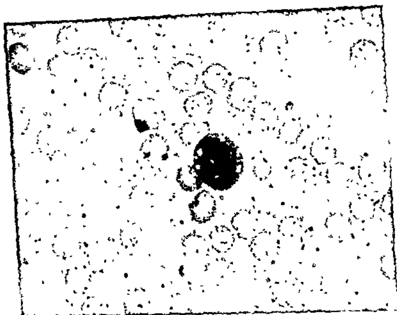


FIG 69—Blood of female mongoloid, 14 months of age (Wright stain, oil immersion) Note primitive, undifferentiated patterns of segmented cells with vacuolization of cytoplasm and nucleus

veal a severe cellular inadequacy of hematopoiesis As figures 67 and 68 demonstrate, the segmentation of blood cells in mongoloid patients is quite incomplete. Figure 67 shows two female blood smears with the drumstick formation. Figure 68 shows two male mongoloid blood smears with minute drumstick-like formations. Although the "drumsticks" are somewhat smaller than in the female, they appear of the same nature Further investigations will decide the significance of these observations Figure 69 shows another aspect which has been rarely observed—the formation of large vacuoles in the cytoplasm and nucleus of segmented cells. Vacuolization in the cytoplasm has been seen
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bined disorder to be anticipated by *chance alone is calculated to be 12 3 for the* four-year period for the same age group in the population at large

The actual occurrence of simultaneous leukemia and mongolism during this period seems therefore approximately three times higher than that which might be anticipated to result from chance association. Since the Scottish research group reported anomalies in the chromosome counts of mongoloids as well as of patients with leukemia, a possible link between the two conditions may be expected.

BIOCHEMISTRY

Table 12 tabulates new biochemical studies on 42 individuals with mongolism ranging in age from 28 years to 21 days. These studies are in addition to biochemical findings reported previously by Bixby and Benda. The serum calciums are essentially within the normal limits (8 to 11.5 mg./100 ml.) established for this method by Schoenthal and Lurie in a study of 250 healthy children. However, this observation is not entirely in line with a study by Sobel et al., who report that mongoloid children show "statistically significant tendencies for lowered serum calcium values, decreased serum albumin, and increased serum gamma-globulin concentrations." Whether the difference is due to variations in food intake cannot be decided, but since our observations are based on a long line of institutionalized patients under strict supervision, it seems to me that the differences in serum calcium are not significant.

The values for inorganic phosphorus are also within the normal range, which is 3 to 4 mg. per 100 ml. for adults and 4 to 6 mg per 100 ml. for children. Likewise, the results for the serum phosphatase activity expressed in *Bodansky* units are within *established normal* limits (1 5 to 4.0 U. per 100 ml for adults and 5 0 to 14 0 U per 100 ml for children).

The values for blood chlorides fall within the normal range, given by Mattice as from 450 to 500 mg. per cent, or 350 to 550 mg per cent according to Osgood, or 441 to 519 mg. per cent according to Karlson and Norberg (76 to 91 mEq./L.).

The values for sodium, serum total proteins, albumin and fibrinogen also appear to be within the normal range. However, our own studies seem to indicate a rather large number of albumin values below the average and the albumin-globulin ratio below the 2 line, with practically all values below 2.5. The above-mentioned study by Sobel et al. also revealed a tendency to decreased serum albumin and increased serum gamma globulin concentration The same authors studied vitamin A absorption and report that mongoloids, both infants

TABLE 12.—*Biochemical Tests on 42 Patients with Mongolism, Ranging in Age from Infancy to 28 Years*

Case no., Sex	Chronol age Yrs	Mos	Days	Ment age Yrs	Mos	IQ	Calcium (mg %)	Inorganic phosphates (mg %)	Alkaline phosphatase (Bodansky U)	PBI (gamma %)	Cholesterol (mg %)	Eosinophils: ACTH (25 mg) (% change)	Eosinophils: Adrenalin* (% change)
1, M	28	4		4	8	29	9.9	4.0	3.6	4.4	175	−15	−37
2, F	27	4		5	8	35	—	—	—	8.4	215	—	0
3, M	26	11		2	10	18	10.4	3.2	1.9	5.6	245	−90	−82
4, M	25	9		2	6	17	8.7	3.4	2.7	5.4	225	−24	−9
5, M	25	5		4	8	29	8.0	3.5	2.3	6.3	195	−77	−24
6, M	23	5		4	0	25	9.4	3.2	2.4	4.3	185	−63	−66
7, F	22	2		5	9	35	8.9	4.3	2.2	6.6	205	−53	−53
8, M	21	3		5	6	34	9.4	4.1	2.4	6.5	195	−57	−21
9, F	20	11		4	10	30	10.6	4.6	1.7	6.2	215	−27	−47
10, M	20	5		5	4	33	8.9	4.1	2.4	7.2	140	−56	−58
	23	5		—	—	—	—	—	—	—	185	—	—
11, M	20	3		3	2	20	10.4	3.4	2.5	3.5	185	−64	−40
12, F	19	11		2	8	17	10.2	3.5	3.0	6.5	295	−66	−37
13, F	19	6		4	6	28	10.0	4.2	3.0	6.9	235	−21	−16
14, M	18	2		2	8	17	9.1	4.3	5.1	5.1	235	−71	−62
15, F	18	1		4	8	30	9.7	3.7	3.0	6.2	220	−16	−18
16, M	17	10		3	4	22	9.1	3.7	3.3	5.4	230	−36	−19
17, M	17	6		3	0	19	9.1	4.0	4.3	—	235	−45	−35
18, F	16	11		5	4	37	—	—	—	5.3	230	−58	−23
19, F	16	11		5	8	40	10.5	4.3	3.2	4.7	235	−35	−64
20, M	16	7		3	8	24	10.0	4.3	4.4	5.4	175	−5	−4
21, M	16	7		4	4	31	10.7	4.3	3.5	5.5	245	−46	−25
22, F	16	0		2	2	16	10.4	4.4	5.5	4.9	230	0	−2
23, M	4	3		0	8(AE)	33(SQ)	9.8	2.8	11.1	4.2	206	—	—
24, F	2	6		0	6	43 (est)	9.7	—	—	4.6	165	—	—
25, M	2	4	15	—	—	—	9.8	—	—	4.6	182	—	—
26, M	2	2		0	6	43 (est)	—	—	—	—	110	—	—
	2	9		—	—	—	9.5	—	—	3.3	140	—	—
27, M	1	6		0	5	28 (est)	5.9	5.1	3.5	5.7	140	—	—
	2	7		—	—	—	4.8	4.6	2.0	—	—	—	—
	2	11		—	—	—	—	—	—	—	—	−47	—
	3	2		—	—	—	9.0	4.5	2.7	—	200	—	—
28, M	1	3		—	—	—	6.0	5.7	5.4	3.5	—	−27	—
29, M	1	0		—	—	—	6.0	5.5	5.5	5.1	155	−39	—
30, M	0	11		—	—	—	9.2	5.3	6.7	2.8	175	—	—
31, F	0	9		0	3	33 (est)	—	—	—	4.7	—	—	—
32, F	0	8		0	4	50	—	—	—	5.1	300	—	—
33, M	0	5	15	0	1	25 (est)	4.1	5.7	2.8	4.0	150	—	—
34, M	0	4		—	—	—	7.0	5.1	Insuff	3.8	165	−38	—
	0	9	21	—	—	—	9.2	—	—	2.6	155	—	—

(*Continued on page 164*)

bined disorder to be anticipated by chance alone is calculated to be 12.3 for the four-year period for the same age group in the population at large.

The actual occurrence of simultaneous leukemia and mongolism during this period seems therefore approximately three times higher than that which might be anticipated to result from chance association. Since the Scottish research group reported anomalies in the chromosome counts of mongoloids as well as of patients with leukemia, a possible link between the two conditions may be expected

BIOCHEMISTRY

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The values for blood chlorides fall within the normal range, given by Mattice as from 450 to 500 mg per cent, or 350 to 550 mg per cent according to Osgood, or 411 to 519 mg. per cent according to Karlson and Norberg (76 to 91 mEq./L.)

The values for sodium, serum total proteins, albumin and fibrinogen also appear to be within the normal range However, our own studies seem to indicate a rather large number of albumin values below the average and the albumin-globulin ratio below the 2 line, with practically all values below 2 5. The above mentioned study by Sobel et al. also revealed a tendency to decreased serum albumin and increased serum gamma globulin concentration The same authors studied vitamin A absorption and report that mongoloids, both infants

TABLE 12 —*Biochemical Tests on 42 Patients with Mongolism, Ranging in Age from Infancy to 28 Years*

Case no., Sex	Chronol. age Yrs	Chronol. age Mos	Chronol. age Days	Ment. age Yrs	Ment. age Mos	IQ	Calcium (mg %)	Inorganic phosphates (mg %)	Alkaline phosphatase (Bodansky U)	PBI (gamma %)	Cholesterol (mg %)	Eosinophils: ACTH (25 mg) (% change)	Eosinophils: Adrenalin* (% change)
1, M	28	4		4	8	29	9 9	4 0	3 6	4 4	175	−15	−37
2, F	27	4		5	8	35	—	—	—	8 4	215	—	0
3, M	26	11		2	10	18	10 4	3 2	1 9	5 6	245	−90	−82
4, M	25	9		2	6	17	8.7	3 4	2.7	5 4	225	−24	−9
5, M	25	5		4	8	29	8 0	3 5	2 3	6 3	195	−77	−24
6, M	23	5		4	0	25	9 4	3 2	2 4	4 3	185	−63	−66
7, F	22	2		5	9	35	8 9	4 3	2 2	6 6	205	−53	−53
8, M	21	3		5	6	34	9 4	4 1	2.4	6 5	195	−57	−21
9, F	20	11		4	10	30	10 6	4 6	1 7	6.2	215	−27	−47
10, M	20	5		5	4	33	8 9	4 1	2 4	7 2	140	−56	−58
	23	5		—	—	—	—	—	—	—	185	—	—
11, M	20	3		3	2	20	10 4	3 4	2 5	3 5	185	−64	−40
12, F	19	11		2	8	17	10 2	3 5	3.0	6 5	295	−66	−37
13, F	19	6		4	6	28	10 0	4 2	3 0	6.9	235	−21	−16
14, M	18	2		2	8	17	9 1	4 3	5 1	5 1	235	−71	−62
15, F	18	1		4	8	30	9 7	3 7	3 0	6 2	220	−16	−18
16, M	17	10		3	4	22	9 1	3 7	3 3	5 4	230	−36	−19
17, M	17	6		3	0	19	9 1	4 0	4.3	—	235	−45	−35
18, F	16	11		5	4	37	—	—	—	5 3	230	−58	−23
19, F	16	11		5	8	40	10 5	4.3	3 2	4 7	235	−35	−64
20, M	16	7		3	8	24	10 0	4 3	4 4	5 4	175	−5	−4
21, M	16	7		4	4	31	10 7	4 3	3 5	5 5	245	−46	−25
22, F	16	0		2	2	16	10 4	4 4	5 5	4 9	230	0	−2
23, M	4	3		0	8(AE)	33(SQ)	9 8	2 8	11.1	4.2	206	—	—
24, F	2	6		0	6	43 (est)	9 7	—	—	4 6	165	—	—
25, M	2	4	15	—	—	—	9 8	—	—	4 6	182	—	—
26, M	2	2		0	6	43 (est)	—	—	—	—	110	—	—
	2	9		—	—	—	9.5	—	—	3 3	140	—	—
27, M	1	6		0	5	28 (est)	5 9	5 1	3 5	5 7	140	—	—
	2	7		—	—	—	4 8	4 6	2 0	—	—	—	—
	2	11		—	—	—	—	—	—	—	—	−47	—
	3	2		—	—	—	9 0	4 5	2 7	—	200	—	—
28, M	1	3		—	—	—	6 0	5.7	5 4	3 5	—	−27	—
29, M	1	0		—	—	—	6 0	5.5	5 5	5 1	155	−39	—
30, M	0	11		—	—	—	9 2	5 3	6 7	2 8	175	—	—
31, F	0	9		0	3	33 (est)	—	—	—	4 7	—	—	—
32, F	0	8		0	4	50	—	—	—	5 1	300	—	—
33, M	0	5	15	0	1	25 (est)	4 1	5 7	2 8	4 0	150	—	—
34, M	0	4		—	—	—	7.0	5.1	Insuff	3 8	165	−38	—
	0	9	21	—	—	—	9 2	—	—	2 6	155	—	—

(Continued on page 164)

bined disorder to be anticipated by chance alone is calculated to be 12.5 for the four-year period for the same age group in the population at large.

The actual occurrence of simultaneous leukemia and mongolism during this period seems therefore approximately three times higher than that which might be anticipated to result from chance association. Since the Scottish research group reported anomalies in the chromosome counts of mongoloids as well as of patients with leukemia, *a possible link between the two conditions may be expected.*

BIOCHEMISTRY

Table 12 tabulates new biochemical studies on 42 individuals with mongolism ranging in age from 28 years to 21 days. These studies are in addition to biochemical findings reported previously by Bixby and Benda. The serum calciums are essentially within the normal limits (8 to 11.5 mg./100 ml.) established for this method by Schoenthal and Lurie in a study of 250 healthy children. However, this observation is *not entirely in line with a study by Sobel et al., who report* that mongoloid children show "statistically significant tendencies for lowered serum calcium values, decreased serum albumin, and increased serum gamma-globulin concentrations." Whether the difference is due to variations in food intake cannot be decided, but since our observations are based on a long line of institutionalized patients under strict supervision, it seems to me that the differences in serum calcium are not significant.

The values for inorganic phosphorus are also within the normal range, which is 3 to 4 mg. per 100 ml. for adults and 4 to 6 mg. per 100 ml. for children. Likewise, the results for the serum phosphatase activity expressed in Bodansky units are within established normal limits (1.5 to 4.0 U. per 100 ml. for adults and 5.0 to 14.0 U. per 100 ml. for children).

The values for blood chlorides fall within the normal range, given by Mattice as from 450 to 500 mg. per cent, or 350 to 550 mg. per cent according to Osgood, or 441 to 519 mg. per cent according to Karlson and Norberg (76 to 91 mEq./L.)

The values for sodium, serum total proteins, albumin and fibrinogen also appear to be within the normal range. However, our own studies seem to indicate a rather large number of albumin values below the average and the albumin-globulin ratio below the 2 line, with *practically all* values below 2.5. The above-mentioned study by Sobel et al. also revealed a tendency to decreased serum albumin and increased serum gamma globulin concentration. The same authors studied vitamin A absorption and report that mongoloids, both infants

TABLE 13—*Calcium, Inorganic Phosphorus, Phosphatase*

Sex	Age*	Calcium (mg %)	Inorganic Phosphorus (mg %)	Phosphatase (Bodansky units)
F	4.11	9.1	5.3	9.8
F	5.6	9.5	4.8	13.4
F	5.8	10.1	4.9	6.1
F	6.5	9.4	5.9	10.1
F	6.5	10.1	4.5	9.2
M	6.8	10.7	5.3	7.4
M	7.6	9.6	5.3	8.3
F	7.10	9.2	5.6	9.0
M	8.3	10.3	4.9	8.1
M	8.6	9.4	5.4	7.6
M	8.11	9.7	5.2	8.7
M	10.4	9.5	4.9	8.2
F	10.4	9.4	5.3	9.7
M	11.0	10.0	4.9	7.8
F	11.7	10.4	4.9	12.2
M	11.10	9.1	5.4	7.6
F	11.11	9.7	4.5	8.9
M	12.9	9.8	5.2	7.0
M	13.1	10.0	4.2	5.8
F	13.9	9.6	4.1	6.1
F	13.9	9.6	4.6	5.7
M	15.6	10.0	5.1	7.7
F	17.0	11.8	3.9	4.3
M	29.6	9.9	3.7	3.5
F	30.2	9.7	3.5	2.9

* Age in this and the following tables is given in years before the decimal point and number of months after

TABLE 14—*Blood Chlorides of Mongoloid Defectives*

Age	Sex	NaCl (mg %)	Age	Sex	NaCl (mg %)
6.0	F	519	17.6	F	535
8.11	M	500	17.8	F	510
9.2	M	523	18.3	F	498
11.1	F	535	19.7	F	530
12.6	M	495	20.3	M	519
12.8	M	542	20.4	M	482
13.6	M	509	22.4	F	506
14.5	F	498	22.9	M	496
14.5	F	522	24.0	F	502
14.7	M	491	24.5	M	501
15.11	F	530	25.9	M	480
16.7	M	489	27.2	F	530
17.4	F	480			

TABLE 12—*Continued*

Case no., sex	Chronol age			Ment age		IQ	Calcium (mg %)	Inorganic phosphates (mg %)	Alkaline phosphatase (Bodansky U)	PBI (gamma %)	Cholesterol (mg %)	Eosinophils	
	Yrs	Mos	Days	Yrs	Mos							ACTH (25 mg) (% change)	Adrenalin* (% change)
35, F	0	3	15	—	—	—	10 1	7.2	7 35	—	160	—	—
36, F	0	3		—	—	—	9.1	—	—	3 6	135	—	—
37, F	0	2	23	—	—	—	7.61	—	—	6 9	—	—	—
	0	5	16	—	—	—	—	—	—	7 0	—	—	—
	2	7		—	—	—	9 0	5.3	3 4	5 3	146	—	—
38, M	0	1	21	—	—	—	—	—	—	6 1	163	—	—
39, F	0	1	15	—	—	—	—	—	—	5 5	—	—	—
	2	3		—	—	—	9 8	4 3	3 8	6 8	204	—	—
40, F	0	1	5	—	—	—	8 7	—	—	5 8	143	—	—
41, F	0	1		—	—	—	9 5	7 2	11 8	10 0	161	—	—
42, M	0	0	21	—	—	—	—	—	—	4 0	—	—	—
	0	3	14	—	—	—	—	—	—	5 3	—	—	—
	2	5		—	—	—	9 8	6 0	3 2	5 8	163	—	—

* Adrenalin chloride, 1:1000 solution 0 3 ml (corrected for body weight)

and young children, exhibit lowered absorption of vitamin A in oil compared with normal infants and children of the same age. In a discussion of the possible significance of this observation, Sobel et al. mention that Bronsch has shown that vitamin A plays a part in the *normal function of the pituitary. Lack of vitamin A prevents* the growth hormone from being fully effective, apparently because of a disturbance of the synthesis of the growth hormone.

Table 15 represents the sodium values of 17 cases, ranging from 3 to 31 years of age. The normal average is given in the textbook of *Gradwohl as 330 mg. per cent sodium, or 143 mEq /L The balance* of sodium is kept rather constant in any blood serum, and the variations from the normal are slightly smaller than those of most substances in the blood. From table 15 it appears that 8 of these 17 values fall between 315 and 320, being 4.5 per cent below average. Six values fall between 321 and 325, being still at the lower edge of normal range. Only 3 of all values fall between 328 and 334, or exactly within the normal range. These facts are worth noticing, because they seem to indicate a *moderate loss of sodium, in contrast to the chlorides,* which were within normal range.

M. and O. Bodansky consider 315 mg. per cent as normal average and a decrease as significant only when below 315. From this point of view, all reported values in mongolism are normal.

TABLE 13.—*Calcium, Inorganic Phosphorus, Phosphatase*

Sex	Age*	Calcium (mg %)	Inorganic Phosphorus (mg %)	Phosphatase (Bodansky units)
F	4.11	9.1	5.3	9.8
F	5.6	9.5	4.8	13.4
F	5.8	10.1	4.9	6.1
F	6.5	9.4	5.9	10.1
F	6.5	10.1	4.5	9.2
M	6.8	10.7	5.3	7.4
M	7.6	9.6	5.3	8.3
F	7.10	9.2	5.6	9.0
M	8.3	10.3	4.9	8.1
M	8.6	9.4	5.4	7.6
M	8.11	9.7	5.2	8.7
M	10.4	9.5	4.9	8.2
F	10.4	9.4	5.3	9.7
M	11.0	10.0	4.9	7.8
F	11.7	10.4	4.9	12.2
M	11.10	9.1	5.4	7.6
F	11.11	9.7	4.5	8.9
M	12.9	9.8	5.2	7.0
M	13.1	10.0	4.2	5.8
F	13.9	9.6	4.1	6.1
F	13.9	9.6	4.6	5.7
M	15.6	10.0	5.1	7.7
F	17.0	11.8	3.9	4.3
M	29.6	9.9	3.7	3.5
F	30.2	9.7	3.5	2.9

* Age in this and the following tables is given in years before the decimal point and number of months after

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35, F	0	3	15	—	—	—	10.1	7.2	7.35	—	160	—	—
36, F	0	3		—	—	—	9.1	—	—	3.6	135	—	—
37, F	0	2	23	—	—	—	7.61	—	—	6.9	—	—	—
	0	5	16	—	—	—	—	—	—	7.0	—	—	—
	2	7		—	—	—	9.0	5.3	3.4	5.3	146	—	—
38, M	0	1	21	—	—	—	—	—	—	6.1	163	—	—
39, F	0	1	15	—	—	—	—	—	—	5.5	—	—	—
	2	3		—	—	—	9.8	4.3	3.8	6.8	204	—	—
40, F	0	1	5	—	—	—	8.7	—	—	5.8	143	—	—
41, F	0	1		—	—	—	9.5	7.2	11.8	10.0	161	—	—
42, M	0	0	21	—	—	—	—	—	—	4.0	—	—	—
	0	3	14	—	—	—	—	—	—	5.3	—	—	—
	2	5		—	—	—	9.8	6.0	3.2	5.8	163	—	—

* Adrenalin chloride, 1:1000 solution 0 3 ml (corrected for body weight)

and young children, exhibit lowered absorption of \itamin A in oil compared with normal infants and children of the same age. In a discussion of the possible significance of this observation, Sobel et al mention that Bronsch has shown that vitamin A plays a part in the normal function of the pituitary Lack of vitamin A prevents the growth hormone from being fully effective, apparently because of a disturbance of the synthesis of the growth hormone.

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TABLE 16 —*Mongoloid Serum Total Nitrogen, Nonprotein Nitrogen and Total Protein*

Age	Sex	TN (mg %)	NPN (mg %)	TP (Gm %)
8 3	M	1106	*	6 75
8 8	M	1135	22	7.02
9 1	M	1061	23	6 49
9 4	M	1099	*	6.72
11 6	M	1045	25	6 38
12 0	F	1122	21	6 88
12 1	F	1064	22	6 51
12 3	M	1114	*	6.81
12 5	M	1196	24	7.32
12 8	F	1135	22	6 96
19 5	F	1188	24	7 28
26 10	F	1110	27	6 77

* NPN assumed to be 25 mg per cent.

method, 4 cases were above 0.50 per cent, which appears pathologic, and 10 other values were above 0 35 Only a single test fell on the 0.30 line The method is unreliable. The tendency to high values of fibrinogen is less marked in the second series, done with the more reliable method of Kjeldahl. In this series case 3 had a constantly elevated value of 0 50 and 0.49, respectively, and 5 other values were 0 35 or more On the other hand, some of the values in the series were low, like that of case 14, with a value of 0.20

The reported serum cholesterols are additional ...

... values of mongoloid children are usually within the normal range except in those ...

... months to 29 years. Fourteen of the 34 males and 17 of the 27 females show values above 200 mg./100 ml, with a few values above 300 Several patients had repeated tests, and all were of the same level In addition, 10 males had values between 180 and 200, and two more females were also above 180 mg per cent. This gives a total of 43 of 61 patients who had cholesterol values above 180 On the other hand, one female mongoloid baby with almost cretinoid features had values of 76, 77 and 80 mg. per cent, respectively, on three occasions.

Results of tests presented in table 19 show the same relation as the

TABLE 15.—*Serum Sodiums*

Age	Sex	Sodium (mg %)	Sodium (mEq/L)	Age	Sex	Sodium (mg %)	Sodium (mEq/L)
3 3	M	325	141	12 8	F	318	138
4 9	F	319	139	14 2	M	324	141
4 11	M	320	139	14 10	F	328	143
5 2	M	321	140	14 10	F	322	140
6.1	F	325	141	16.7	M	332	144
7 9	M	315	137	18 1	F	321	140
8 11	F	319	139	24 0	F	334	145
9 4	M	318	138	31 3	F	315	137
11 6	F	319	139				

Range 315 to 334 mg per cent, or 137 to 145 mEq/L

The serum total proteins shown in table 16 for 12 mongoloid patients from 8 to 26 years of age are within normal limits, being 6 4 to 7.3 Gm. per cent (normal: 6 to 8 Gm per cent).

Although the total proteins fall grossly between the normal average range of 6 to 8 Gm. per cent, it is noteworthy that in this series all but 3 values are below 7, and only 3 fall between 7 and 7.3 Gm. per cent. None of the values conteracts the low tendency seen in this series. It was, however, felt that the values may not be representative for a larger group, and that more information was needed

In table 17, 38 more total protein values are recorded. About half of them were done by the Kjeldahl method, the others by the Kingsley biuret method. Kjeldahl values range between 6.67 and 7 90, the average being 7.35. The values seem slightly lower than average. One may possibly conclude that there is a trend toward low values, but the result is still well within normal range and the significance is, therefore, not statistical.

In the same series of tests, with the use of the Kingsley-Kjeldahl method, the albumin averaged 4.93 Gm per cent, with values ranging from 4.65 to 5.48. In the same test series done by this method, the globulins ranged from 1 93 to 2.89, with an average of 2.44 If one considers 2.5 Gm. per cent as a fair average, it is obvious that very few values are above this line, but many values are below. The albumin-globulin ratio is debatable. A number of cases fall below the 2 line, and practically all values remain below 2 5, but all seem to be within normal range.

The fibrinogen is high by both the Andersch-Gibson method and the Kjeldahl method In a series of 15 tests done with the former

TABLE 18.—*Values of Total Cholesterol of Serum during Fasting*

Male		Female	
Age	Cholesterol (mg /100 ml)	Age	Cholesterol (mg /100 ml)
2 9	218	3 8	269
2 10	227	3.10	308
3 3	205	4.9	195
3 3	192	{4 3	{76
3 10	278		80
4 11	219		77
5 2	204	4 6	320
7 1	140	5 0	200
7 6	180	6 1	245
7 9	188	6 7	219
8 0	247	7 1	179
8 2	163	7.5	215
9 8	189	8 6	220
10 4	198	9.2	234
{10 4	{312	10 0	170
10 7	291	11.3	248
10 9	244	11 4	152
10 10	144	11 5	170
11 2	205	11 6	178
12 2	223	11 6	168
12 3	170	13 2	228
12 3	202	14 0	197
13 5	191	14 1	224
13 9	173	{15 8	{248
14 6	206	16 5	236
14 7	149	17 7	163
15 8	151	17 11	135
16 11	150	18 1	140
17 3	181	20 3	217
17 7	201	{25 3	{268
18 5	192	26 0	254
19 5	196	{27 8	{248
22 6	155	28 5	254
23 3	207	29 0	234
23 10	140		
27 9	194		

values for the controls between the total cholesterol and the cholesterol esters of whole blood and of serum. It is seen that the values for total cholesterol in the whole blood and in the serum are not nearly as equal and interchangeable as might be inferred from the literature. The total cholesterol in the blood tends to be nearer or equal to the total in the serum when it is low. The percentages of

TABLE 17.—*Serum Proteins of Mongoloid Defectives*

No	Sex	Age		Total Prot (Gm. %)		Albumin (Gm %)		Globulin (Gm %)		Fibrin (Gm %)	Alb /Glob by Diff		Explanation of symbols and remarks
		Yr	Mo	Kj	K-B	K Kj	K-B	K Kj	K-B	Kj	K-Kj	K-B	
2	F	2	6	—	6 25	—	4 89	—	1 36	0 25	—	3 60	Serum unless otherwise indicated
		2	7	6 67	—	4 65	4 50	2 02	—	0 29	2 30	—	Fibrins on oxalated plasma
3	F	3	1	—	6 53	—	4.85	—	1 68	—	—	2 89	Total proteins are without fibrin
		3	2	7 58	—	5 11	5 05	2 47	—	0 50	2 07	—	Globulins by difference, without fibrin
		3	2	7 76	7 73	5 28	5 08	2 48	2 65	0 49	2 13	1.92	K—Kingsley separation
4	M	3	1	—	6.76	—	5.13	—	1 63	0 29	—	3 15	Kj—Kjeldahl analysis
		3	2	6 86	6 91	—	5 07	—	1 84	0 30	—	2 76	B—Kingsley biuret analysis
5	M	3	10	—	5 85	—	4 72	—	1 13	0 25	—	4 18	*—0 1 ml. serum used instead of 0 08 ml.
		3	10	6 85	—	4 92	4 65	1 93	—	0 35	2 55	—	h—Heparinized plasma
6	M	5	0	7 42	7 48	4 77	4 85	2 65	2 63	0 29	1 80	1 84	H—Howe separation
7	M	5	9	7 54	7 65	4 75	4 68	2 79	2 97	0 31	1 70	1 58	x—oxalated plasma
9	F	9	8	7 04	6 86	4 92	4 85	2 12	2 01	0 27	2 32	2 41	
10	M	13	8	7 48	7 17	—	4 95	—	2 22	0 39	—	2 23	
		13	*9*	7 50	7 46	5 05	4 99	2 45	2 47	0 35	2 06	2 02	
11	M	13	11	7 35	—	4 93	—	2 42	—	0 27	2 04	—	
12	F	15	9	7 26	6 90*	4 76	4 85	2 50	2 05	0 28	1 90	2 37	
13	M	16	3	7 01	6 78	4 78	4 72	2 23	2.06	0 27	2 14	2 29	
14	F	16	7	7 58	7 60*	4 96	4 92	2 62	2 68	0 20	1 89	1 84	
16	M	18	8	7 53	7 62*	4 84	4 78	2 69	2 84	0 34	1 80	1 68	
17	F	21	0	7 90	7 72*	5 48	5 41	2 42	2 31	0 28	2 26	2 34	
18	M	27	0	6 72h	—	4 40h	—	2 32h	—	0 24	1 90h	—	
				6 14x		4 03Hh							
19	F	28	7	7 70	7 37*	4 81	—	2 89	—	0 28	1 66	—	
20	F	32	1	7 24h	—	4 60h	—	2 64h	—	0 35	1 74h	—	
				6 90x		4 44Hh							
Low				6 67		4 65		1 93			1 66		Excluding nos 18 and 20
High				7 90		5 48		2 89			2 55		" " " " "
Average				7 35		4 93		2 44		0 30	2 04		" " " " "

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normals lowest " Because of these extremely interesting observations, Benda and Mann examined a group of mongoloids for the purpose of either confirming the observations or finding a different explanation A study of 54 subjects with mongolism revealed but little evidence of the serum lipid pattern characteristic of mongolism When the mongoloid groups were compared with the institutional controls, only the female mongoloids under 25 years of age showed a persistent tendency to higher lipoprotein and cholesterol levels. All the male mongoloids and the female mongoloids of 25 years or more showed irregular higher or lower levels of these lipids than did the institutional controls Furthermore, the absolute levels of these serum lipids were not greatly different in the defective groups from those of the normal population It is clear that these serum lipid measurements cannot serve as a means to discriminate between such groups, much less to characterize individuals. There is little evidence from these measurements that mongolism is characterized by alterations of serum lipid patterns

With regard to the consistent and yet—in their specific character—inconsistent patholo-

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whether the

...ous from table 12, the majority of cases show values within the accepted range (from 4 to 8) Only occasional cases show low protein-bound iodide values, and again they seem to be cases in which there is definite evidence of hypo- or dysthyroidism While these cases are not too rare, the large number of patients with PBI values within the normal range indicates that sufficient protein-bound iodide is circulating, but the findings do not show that the globulin fraction itself is normal

Further insight into thyroid function in mongolism has been expected from radioisotope studies carried out by a number of investigators Hofmann-Credner and Zu...

TABLE 19.—*Total and Esterified Cholesterol Values of Serum and of Whole Blood of Mongoloid Patients*

Subject	Sex	Age Yr	Age Mo	Cells (%)	Total serum cholesterol (mg)	Total blood cholesterol (mg)	Serum ester (mg)	Serum ester %	Blood ester (mg)
1	M	2	10	—	227	—	144	62	—
					227	—	137	—	—
2	M	7	9	41	188	171	124	68	69
					188	170	129	—	68
					186	—	128	—	—
3	M	10	7	46	291	233	206	70	84
					283	234	194	—	81
		10	9	46	244	200	196	80	114
						201	—	—	107
4	M	12	2	—	218	193	—	—	—
					227	191	—	—	—
5	M	13	5	45	189	165	116	61	56
					191	165	116	—	59
					191	—	109	—	—
6	F	17	11	40	130	145	88	66	53
					133	148	88	—	55
						149	—	—	—
		18	1	41	140	141	103	74	56
					140	140	103	—	—
7	M	18	5	—	195	164	—	—	—
					189	169	—	—	—
8	M	23	10	—	140	140	—	—	—
					140	140	—	—	—
9	F	29	—	—	233	191	—	—	—
					234	199	—	—	—

ester in mongoloid serum, varying from 61 to 80, were about the same as those in controls, 57 to 71. These results correspond with published data for normal plasma or serum.

Reports in the literature on cholesterol in general are conflicting, and those on infants are meager and questionable. It is said that normally at birth the cholesterol of the child is much lower than that of the mother. According to Palacios-Costa and Falsia, the average total cholesterol of umbilical cord blood is 108 mg per cent and independent of the maternal level. It is difficult to learn at just what age the value may reach a fairly constant level for the individual. Offenkrantz and Karshan give the total serum cholesterols of 19 boys and 11 girls of from 2 months to 3 years of age as 174.1 ± 45.3 mg. per cent (128.8 to 219.4 mg. per cent) and for 51 boys and 40 girls of from 4 to 6 years as 177.5 ± 30.4 mg. per cent (147.1 to 207.9 mg. per cent). These au-

thors used the Schoenheimer-Sperry method (modified), which is said to be 5 to 15 per cent lower than the Sackett procedure (Mattice), which in turn has been found to check very closely with the modified Bloor method, used in our laboratory.

While the values of serum cholesterol do not reveal significant anomalies, Simon et al reported most marked differences between mongoloids, normal and control children "in the level of large molecule lipoproteins of the S_f 12–20 class, the mongoloids being highest, the cases of undifferentiated mental deficiency intermediate, and the normals lowest." Because of these extremely interesting observations, Benda and Mann examined a group of mongoloids for the purpose of either confirming the observations or finding a different explanation. A study of 54 subjects with mongolism revealed but little evidence of the serum lipid pattern characteristic of mongolism. When the mongoloid groups were compared with the institutional controls, only the female mongoloids under 25 years of age showed a persistent tendency to higher lipoprotein and cholesterol levels All the male mongoloids and the female mongoloids of 25 years or more showed irregular higher or lower levels of these lipids than did the institutional controls Furthermore, the absolute levels of these serum lipids were not greatly different in the defective groups from those of the normal population It is clear that these serum lipid measurements cannot serve as a means to discriminate between such groups, much less to characterize individuals. There is little evidence from these measurements that mongolism is characterized by alterations of serum lipid patterns

With regard to the consistent and yet—in their specific character—inconsistent pathologic observations on the thyroid in mongolism, a number of investigators have examined the question of whether the protein-bound iodide is abnormal As is obvious from table 12, the majority of cases show values within the accepted [illegible]
8) [illegible]

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Further insight into thyroid function in mongolism has been expected from radioisotope studies carried out by a number of investigators Hofmann Credner and [illegible]

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					227	—	137	—	—
2	M	7	9	41	188	171	124	68	69
					188	170	129	—	68
					186	—	128	—	—
3	M	10	7	46	291	233	206	70	84
					283	234	194	—	81
		10	9	46	244	200	196	80	114
						201	—	—	107
4	M	12	2	—	218	193	—	—	—
					227	191	—	—	—
5	M	13	5	45	189	165	116	61	56
					191	165	116	—	59
					191	—	109	—	—
6	F	17	11	40	130	145	88	66	53
					133	148	88	—	55
						149	—	—	—
		18	1	41	140	141	103	74	56
					140	140	103	—	—
7	M	18	5	—	195	164	—	—	—
					189	169	—	—	—
8	M	23	10	—	140	140	—	—	—
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These data were again discussed by Freedberg et al., who are of the opinion that

the thyroid glands of mongoloid subjects showed a significantly faster effective half life or decrease in radioactivity than those of a euthyroid control group. Furthermore, a possible abnormality of the plasma protein-thyroid hormone complex in mongolism was suggested by an increase in vitro red cell "uptake" of I^{131} labeled triiodothyronine from whole blood

Five patients had paper-chromatographic studies of blood serum after intake of I^{131} in order to determine whether there were abnormalities of the plasma-protein-thyroid-hormone complex.* "Under the conditions employed, there was no evidence of any compound other than iodide, and no abnormal iodinated protein compounds were found in 4 of the 5" One case was suggestive. Further research is necessary.

The last column of table 12 shows the response to pituitary adrenocorticotropic hormones as a test for a possible deficiency of the adrenal cortex In normal individuals with no adrenal insufficiency, an effect on the number of eosinophils is observed after a single intramuscular injection of 25 mg ACTH. A profound drop in the number of circulating eosinophils (ranging from —49 to —98 per cent) is expected. In pituitary insufficiency, the injection of epinephrine will not stimulate the production of ACTH so that no drop occurs in the eosinophils Eosinopenia may occur, however, following the injection of ACTH itself unless secondary atrophy of the adrenals has occurred

As the last two columns of table 12 indicate, the response to the injection of adrenaline was below the normal range of about —49 to —98 per cent in 13 cases, with no response in 1, 3 low responses (—2, —4 and —9) and 9 cases having values between —10 and —40 The response to the injection of ACTH was low in 7 cases, indicating that there was a difference in response to adrenalin and ACTH in 6 cases In 5 cases the response was below normal in both columns, whereas in at least 4 cases there was an adequate response to ACTH while the response to adrenaline was low This may indicate a possible pituitary hypofunction in 13 cases, with primary or secondary adrenocortical hypofunction in 6 cases In 2 cases there seemed to be a normal response to adrenalin but a subnormal response to ACTH.

These statistics add evidence to the amazing variability of pathologic findings in the pituitary and adrenals, as reported in the section

* The study was done through the courtesy of Dr. John B Stanbury at the Thyroid Laboratory of the Massachusetts General Hospital

with a group of normal and cerebral palsy children. Moreover, the plasma activity (D%1) was remarkably reduced or nonexistent These authors felt that the results were consistent with a secondary hypothyroidism, possibly due to lack of thyrotropic hormones, caused by malfunctioning of the pituitary.

Very careful attention has been given to the problem by Kurland et al., who reported

> no difference in the 24 hour thyroidal I^{131} uptake, conversion into butanol-extractable material, and urinary I^{131} excretion in mongoloids as compared with
> ie age group . In contrast to these
> irnover was found to be significantly
> id controls Since the observation of
> a normal 24-hour I^{131} uptake might
> be explained by the assumption that significant turnover and loss of I^{131} by the thyroid had occurred before the 24-hour measurement, we studied 3 mongoloid patients at five and at twenty-four hours after a tracer dose of I^{131} In these 3 patients, the 5-hour uptake averaged 17 per cent, and the 24-hour uptake averaged 35 per cent The apparent discrepancy between rapid thyroidal I^{131} turnover rate and normal serum protein-bound iodine concentration has also not been resolved If peripheral utilization of thyroid hormone were increased in the same degree as thyroid hormonal release, an equilibrium would be established maintaining the amount of hormone in the blood at a normal level The normal turnover time of plasma thyroxine observed in 2 mongoloid children does not *support the hypothesis of altered peripheral utilization* These findings of an increased thyroidal turnover of iodide and a normal plasma protein bound iodine concentration are consistent with the hypothesis that thyroid function *in such individuals resides in only a small portion of the gland working* at an increased rate, with consequent normal total iodine uptake, a more rapid turnover, and the effective maintenance of a normal level of serum hormone

This explanation seems indeed the more pertinent since the large anatomic material available for study has proved time and again that not a single case showed a thyroid which could be considered normal in every sector of the tissue *We always find areas with extended follicles alternating with hypoplastic sections in which the* colloid production seems definitely inadequate.

> The *other abnormality of thyroid function observed in this study* [Kurland et al] was an increased erythrocytic uptake of triiodothyronine (average 17 3 per cent) Such elevated values have previously been found in thyrotoxicosis None of these patients *had any of the stigmata of hyperthyroidism and, with the exception* of thyroidal I^{131} turnover, other parameters of thyroid function were normal . . Further studies are necessary to clarify the significance of the observation in mongolism, *which may indicate an alteration of the plasma protein* thyroid hormone complex or a plasma factor(s) affecting the tissue uptake of thyroid hormone.

the male values are within the normal range though relatively low, with only two values of 15 mg./24 hours and above. It is noteworthy that three of the female values are above the normal range, falling in a male distribution. On the other hand, 23 of the females over 15 years show values below the normal female range The values correspond to those found in normal children between 10 and 14 years and seem to indicate that there has been an arrest on a pre-puberty level of those glandular tissues which produce the 17-ketosteroids.

Table 20 shows studies of 17-ketosteroids and 17-hydroxycorticoids on 29 patients, with corresponding creatinine values. Only 12 hour specimens could be collected in some cases, but the 12 hour specimens appeared usable since no striking differences between night and day specimens could be observed. For comparison purposes, the reported 17-ketosteroid and 17-hydroxycorticoid values should be doubled in those cases which are marked "12 hour"

BLOOD SUGAR AND GLUCOSE TOLERANCE

The fasting blood sugar values of 51 persons with mongolism, five to 29 years of age, were normal, ranging from 69 to 113 mg. per 100 cubic centimeters of capillary blood (table 21) However, dextrose tolerance tests on 10 mongoloid children (fig. 71) indicated a delayed glycemic response. There seems to be a tendency for a late peak, for a low curve, for a slow return to the fasting level, or for a combination of these After three hours, the single curve (9) with a fairly high peak at the half-hour interval was still 28 mg above the fasting level Sugar was not found in the urine of any of these subjects. In a case (4) in which there was a high late peak, no urine was voided. For comparison, tolerance curves of four controls are presented

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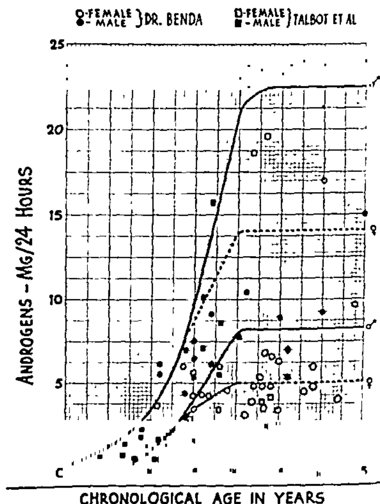


Fig 70 —17-Ketosteroid values in mongolism (51 females, 19 males, for details, see text)

on pathology. There is no consistency of observations which is true for each case of mongolism, but the endocrine deficiency varies as much as the anatomic features and the clinical symptoms

Figure 70 shows 70 17-Kerosteroid values in mongolism (51 female, 19 male) according to chronologic age, placed within the ranges for normal males (solid line) and females (interrupted line). These values have been further increased by including 15 results published by Talbot and co-workers It will be seen that most of the values for children below 15 years of age fall within the normal range, with two high values for males, seven values for females and one for a male below the normal range.

At the age of 15 years, when a gradual transition occurs in the normal individual through the maturation of the gonads, most of

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Inasmuch as one can come to a definite conclusion only after accumulating data from many cases, five more glucose tolerance tests of mongoloid children are added herewith (table 22) to the 10 cases above Again one observes evidence of delayed glycemic response, such as a low or late peak or a relatively slow return to the fasting level, thus confirming Brousseau's statement that there is a high sugar tolerance in mongolism However, in two of the three year olds tested, this evidence does not seem so marked.

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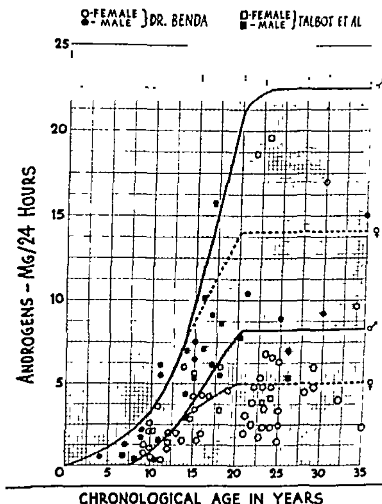


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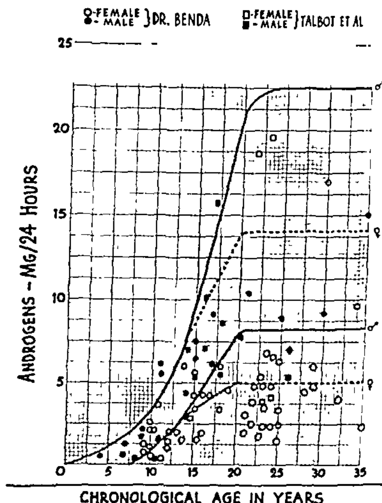


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TABLE 20—*Creatinine and Steroid Values in 24 Hour Urine Specimens*

Case no	Sex	Ca	Weight (lbs)	Total volume (ml) (24 hr specimen)	pH	Creatinine	17-KS*	17-OH†
1	F	41–5	110	1560	5.0	972	1.71	0.99
2	M	38–3	130	825	6.0	42.6§	—	5.95
3 (1)	M	33–1	108	2690	6.0	955	—	0.35
4	M	29–9	138	1850	—	892.6§	—	4.91
5	F	28–4	128	3560‡	5.5	727	3.91	4.02
				3900‡	6.0	584	4.43	3.78
6	M	27–7	151	5530	5.5	13.3§	—	6.64
7	F	25–0	133	605‡	5.5	470	1.56	1.075
				635‡	6.5	289	1.63	1.24
8 (12)	F	24–8	92	730	5.5	1070	—	6.51
9	F	23–3	100	3360	5.5	1655‖	3.53	6.23
10 (15)	F	22–10	121	740	5.5	1175	—	5.16
11	F	22–4	130	2920	7.0	926§	1.77	2.92
12 (17)	M	22–3	150	3000	—	—	—	10.3
13 (19)	F	21–8	106	1755‡	5.5	483§	1.67	0.85
				3800‡	5.5	697§	3.91	4.90
14	F	21–4	130½	2580	5.0	1280	2.49	2.48
15 (22)	F	20–9	90	920	6.0	611§	—	6.9
16	F	16–8	128	2125	—	1168	—	4.03
17	F	15–3	81	670‡	5.5	421	1.51	1.51
				435‡	5.5	275	1.45	0.276
18	F	14–8	129½	2570‡	5.5	826	2.89	3.73
				1220‡	6.0	440	1.60	0.59
19	F	13–9	113	970	5.5	1008	6.0	1.95
20	F	12–3	65	1050	5.5	584§	0.897	1.25
21	F	12–3	68	1400‡	—	437	—	2.29
				275‡	—	235	—	1.35
22	M	10–3	44	740‡	—	344§	—	0.85
				285‡	—	154§	0.478	0.246
23	F	10–0	50	680	—	296.4§	—	0.47
24	F	9–11	69½	830	6.0	533§	2.11	2.51
25	F	9–10	55	510‡	5.5	320§	0.647	0.83
				205‡	7.0	174§	0.589	1.11
26	F	9–8	64	370‡	7.5	171§	0.459	0.358
				1020‡	6.0	493§	1.31	0.99
27	M	8–11	51½	530‡	—	192.5	—	2.13
				190‡	—	150	0.369	0.295
28	M	8–1	65	620	—	255.6§	—	1.747
29	M	6–10	47½	585‡	—	310§	—	6.91
				350‡	—	181§	0.51	1.09

* 17-ketosteroids
† 17-hydro-oxycorticoids
‡ 12 hour specimen
§ Low
‖ High

TABLE 21—*Fasting Blood Sugar Values of Persons with Mongolism*

Sex	Age		Blood Sugar (mg./100 ml.)	Sex	Age		Blood Sugar (mg./100 ml.)
	Yr	Mo			Yr	Mo	
F	5	3	92	F	13	6	95
M	5	4	69	F	14	2	84
M.	6	5	93	F	14	8	94
M	6	10	75	F	14	11	109
M	6	11	85	F	15	0	97
M	7	2	111	F	{15	0	{84
M	7	5	98		{15	1	{94
M	7	6	85	F	{15	1	{101
M	7	7	88		{15	2	{96
F	{7	8	{78	M	{15	6	{83
	{7	9	{82		{15	7	{82
M	7	10	94	M	17	4	101
M	7	11	105	F	17	6	94
M	8	5	108	M	18	5	86
M	8	6	77	F	18	5	94
M	9	3	88	F	{18	5	{91
F	9	8	91		{18	6	{77
M	10	1	79	F	19	4	87
F	10	5	94	M	19	5	97
F	10	5	92	F	21	9	101
M	10	7	93	F	21	9	102
M	10	10	93	F	{22	5	{103
M	11	9	80		{22	6	{99
F	11	9	99	F	23	0	90
M	12	0	99	F	23	5	103
F	12	7	93	M	23	11	100
M	{12	9	{78	F	24	8	95
	{12	10	{84	F	28	5	95
M	13	4	77	F	29	0	113

In most instances, instead of showing a normal drop [illegible]
second half [illegible]

The insulin tolerance curves, both of the mongoloid patients and of the controls, all indicated fasting levels within normal range, although three of the control values were higher than all others (figs. 73, 74 and 75) After insulin, with one exception, the blood sugars responded normally, falling in 20 to 30 minutes to about one-half of the fasting levels At this point, both the mongoloid and the control curves promptly rose again. However, two hours after insulin, when (according to Fraser, Albright and Smith) the blood sugars

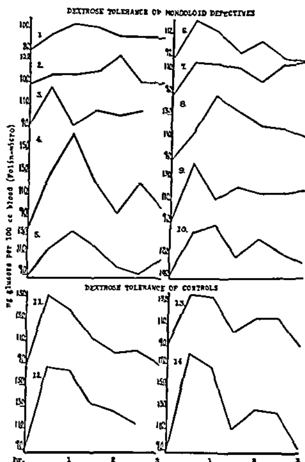


Fig 71.—Dextrose tolerance curves, mongolism and controls The figure indicates delayed glycemic response There is a tendency for late peak, for a low curve, and for slow return to the fasting level Only curve 9 shows a fairly high peak at the half-hour interval, but it also shows a slow return to the fasting level after 3 hours

Table 22 —*Glucose Tolerance in Mongoloid Defectives*

Age		Sex	Min after Glucose						
			0	30	60	90	120	150	180
Yr.	Mo.		Mg % Blood Sugar						
3	4	M	90	103	124	113	101	104	75
3	10	F	98	165	175	140	125	129	103
3	10	F	80	135	84	109	88	106	86
10	5	M	94	144	134	130	120	122	80
12	0	M	85	145	145	132	90	109	89

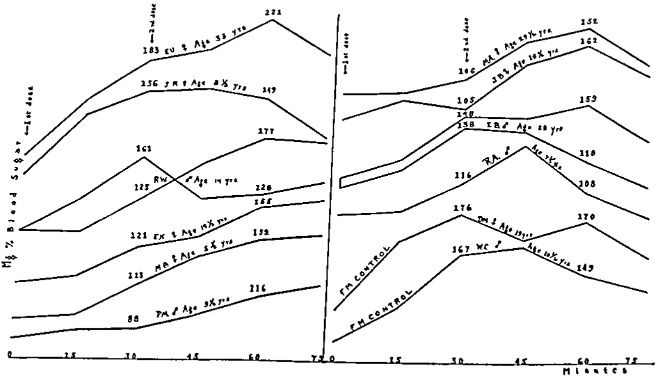


Fig. 72—Exton Rose divided dose, one hour test in mongolism. In most instances the blood glucose continued to rise after the second half dose instead of falling.

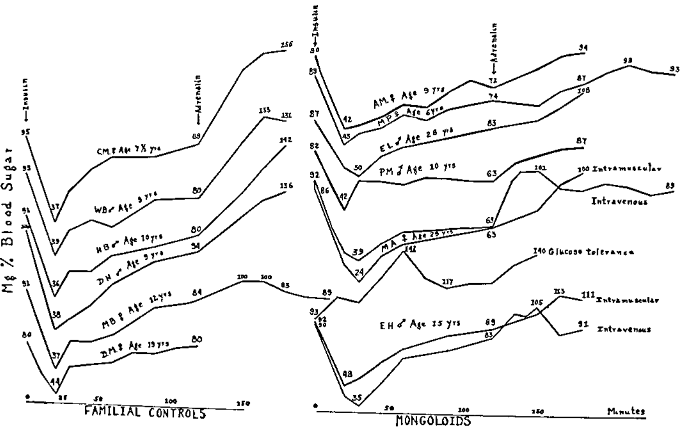
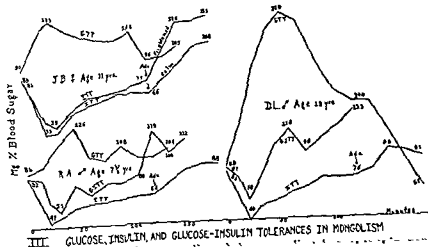


Fig 73 —Insulin tolerance in mongolism After insulin the blood sugars responded normally, falling to about half the fasting level in 20 to 30 minutes At the end of the 2 hour period the blood level was still below fasting levels Adrenalin injections at the end of 2 hours produced much less effect than in normal controls



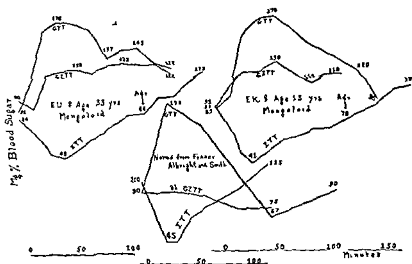


Fig 75 —Glucose, insulin and combined glucose-insulin tolerance tests in mongolism compared with the normal In these two cases of mongolism the effect of the sugar was stronger than that of the insulin and the combined curves ran above normal

should have returned at least to the fasting level, the control values were slightly (0 to 12 and 15 mg.) *below the fasting levels while the* mongoloid values were, with few exceptions, even lower (13–29 mg). At the end of two hours, the absolute values of the mongoloid levels were 63 to 83 and 89 mg. per cent, while those of the controls were 80 to 94 mg. per cent.

At the end of two hours, adrenalin was given intramuscularly. Normally one would expect the blood sugar to respond during the following hour by rising considerably above the fasting level. For four of the controls, this effect amounted to 42, 53, 62, and 67 mg. per cent, whereas for the mongoloid cases, the rise was 13 to 37 and 42 mg. per cent. During the hour following the administration of adrenalin, the highest actual levels reached by the four controls were 133 to 156 mg per cent, while corresponding levels for the mongoloids were much lower—87 to 108, 113 and 123 mg. per cent.

Along with some individual graphs of the insulin tolerance tests, corresponding glucose tolerance and glucose-insulin tolerance curves are also presented The Fraser, Albright and Smith normal curve is shown for comparison (fig. 75)

We can conclude that in 10 of the 11 cases of mongolism, the reaction to insulin was not unusual. Next, we note that all of the curves *rose promptly after 20 to 30 minutes. This indicates that the* response to the hypoglycemia was prompt.

At the end of two hours, however, the blood sugars of the mongoloids *tended to be definitely lower than when fasting and* lower than the corresponding levels of the controls. It would seem, then, that the response is more clearly demonstrated by the administration of adrenalin at two hours, for during the subsequent hour, the control blood sugars rose to values of 133 to 156 mg per cent, while the mongoloid levels rose only to 87 to 123 mg. per cent.

This decreased effectiveness of adrenalin could have various explanations. Comparison of the effect of intramuscular and intravenous injections in two cases of mongolism (curves "M.A." and "E.H.") proves that this decrease is not due to slower absorption of adrenalin from the tissues The increases in blood sugar after intravenous injection are prompter than those after intramuscular injection, although they are practically identical, namely 38 vs 37 mg per cent and 22 vs. 23 mg. per cent, respectively The results of intravenous injection also tend to rule out explanations based on poor circulation of the blood Another possibility is that the effect is due to some specific defect of the autonomic nervous system resulting in the failure of the adrenalin to elicit a normal response. According

to Joedicke, mongoloids have a lessened response to many drugs However, in their clinical reactions, the mongoloids seemed sensitive to both insulin and adrenalin, reacting to the insulin even more and for a somewhat longer time than the controls, exhibiting a more prolonged period of sleepiness and sweating, an increased temperature, a desire to urinate and, in some cases, tremor. After intravenous injection of the adrenalin, two mongoloids showed immediate marked temporary reactions such as extreme pallor, gagging, discomfort, fear and accelerated pulse Thus both the insulin and the adrenalin elicited definite responses.

A possible explanation of the relative ineffectiveness of the adrenalin in mongolism is that it is due to insufficient stores of glycogen in the liver and inability of the liver to release these stores The former view is supported by [illegible]

liv [illegible]

to [illegible]

[illegible] (increased sugar tolerance).

While the insulin tolerance curves as a whole indicate a tendency to a uniformly decreased ability of the mongoloid organism to raise the blood sugar levels, the glucose tolerance curves are as variable and unpredictable as in acromegaly. According to Fraser et al, in acromegaly this variability is due in part to the combined effects of increased growth hormone of the pituitary lowering the blood sugar, and sometimes a compensatedly increased glycotropic hormone, resisting the insulin action

I question whether the high glucose tolerance curves in acromegaly may not be due in part to a decreased ability of the liver to store glycogen, this function having suffered from the originally low blood sugars, owing to excessive thyroid hormones In considering the causes of a hypothetical liver deficiency in mongolism, since there is decreased responsiveness to both hyperglycemia and hypoglycemia, it is suggested that the corticotropic hormone of the pituitary and the adrenal cortical hormone are at fault. The latter hormone, which is stimulated by the former, is the regulator of [illegible]

and [illegible]

[illegible] blood sugar levels to be within normal limits However, she noticed an unusually wide range of values Thirteen per cent of the 127 patients had a fasting blood sugar under 60 mg. per cent Only 3 per cent had a fasting blood sugar greater than 120 mg per cent. Forty-eight per cent of the glucose tolerance curves were found to fall within normal limits

In the other 52 per cent that were abnormal, three configurations were noticed. One abnormality consisted of a very high peak in the blood sugar level following the intravenous injection and then a fall to the fasting level within 60 minutes. Fifteen of the abnormal curves showed a high peak in the curve following the intravenous glucose, with a delayed drop to the fasting level. Forty-one of the abnormal tests consisted of a delayed drop to the fasting level without a high peak. Runge also found that.

> The galactose tolerance test is abnormal in a high percentage of Mongoloids with abnormal glucose tolerance tests The insulin tolerance tests in such patients show a delay in return to initial level. The epinephrine tolerance test shows a suggestion of decrease in response to epinephrine with increasing age

These new observations add further evidence to the conclusion that the high percentage of abnormal curves indicates the great number of individual cases of mongolism that are associated with a widespread metabolic disorder. Taken together with the pathologic observations and other biologic tests, there is evidence that the "molecular" disorder associated with mongolism often manifests itself in early fatty degeneration of the liver, anomalies of the adrenals, abnormal thyroid functioning and gonadal dysfunction. The frequent disturbance of general fat metabolism with obesitas is well known. The sugar tests in individual cases may be helpful in gaining further insight as to which organ systems are especially inadequate in each specific instance

BASAL METABOLISM

The importance of basal metabolism in hypothyroidism and cretinism is so well established that there is no need to discuss the matter in detail. In cretinism the values range usually between −20 and −50 per cent. It is noteworthy that the lowering of the metabolic rate seems frequently less pronounced in thyroidaplastic congenital cretins, while the most outstanding values are seen in postoperative or spontaneous myxedema of adults. A few values which corroborate those published by others are reported in table 23 and in figure 76. Results in mongolism are also reported in table 23 and additional ones in figure 76 The metabolic rate is definitely lowered in mongolism and falls between the level of normal living and cretinism.

Results

When based on the Mayo Foundation standards, the basal metabolic rates of 25 persons with mongolism were on the minus side (table 23). None were plus, 8 were between 0 and −10 per cent, 8

TABLE 23.—*Basal Metabolic Rates of Persons with Mongolism**

Subject	Sex	Age		Height (in.)	Weight (lb.)	O₂ cc per min.	Cal per 24 hr	Metabolic Rate, %			No. of Tests	Cholesterol (mg per 100 ml serum)
								Mayo	Talbot			
		Yr	Mo						Wt	Ht		
1	F	6	1	40½	39	98	681	−22	−14	−10	2	219
2	F	6	1	40	33	107	744	−8	+4	0	2	245
3	M	6	8	42	38½	122	—	−9				
		6	11	42¼	38	121	841	−9	+7	+3	4	140
4	F	7	0	43½	47	121	—	−12				
		7	0	43½	47	120	834	−13	−5	+3	2	215
5	F	7	1	41¼	38½	105	730	−14	−7	−5	4	179
6	M	7	6	47½	55	155	1,077	−8	+5	+14	5	180
7	M	7	9	44½	43	119	827	−18	−3	−2	2	188
8	M	8	1	44½	46	127	—	−13				
		8	2	44½	46	128	890	−14	−1	+4	3	247
9	M	8	2	46	52	128	—	−18				
		8	2	46	52	119	827	−24	−11	−5	2	163
10	F	8	6	42	41	93	646	−24	−21	−17		
		8	6	42	40½	99	688	−18	−15	−12	2	220
11	F	9	1	44¼	43½	110	764	−13	−10	−8		
		9	1	44¼	43½	113	—	−10	—	—	2	234
12	F	9	0	42	46	112	778	−10	−11	−1		
		9	7	42	46	116	—	−7				
		9	7	42	46	115	—	−8	—	—	4	170
13	M	10	2	48½	60	149	—	−9				
		10	2	48½	60	140	973	−14	−11	+1	2	189
14	M	10	3	49½	58	134	—	−20				
		10	3	49½	59	128	899	−22	−18	−10	2	198
15	M	10	7	52	65½	147	—	−16				
		10	7	52	66	144	1,000	−18	−12	−6	2	312
16	F	10	9	50¼	58	133	924	−15	−7	−4	2	248
17	F	10	11	50¾	61	155	—	−4				
		10	11	50¾	62	156	—	−4				
		11	2	51¾	66	161	1,119	−4	+5	+11	4	152
18	F	11	0	52½	79	154	—	−15				
		11	0	52½	80	143	994	−22	−16	−3	2	168
19	M	11	1	48½	58	135	938	−15	−13	−3	3	205
20	F	11	6	49	56	119	827	−21	−15	−12	2	178
21	M	12	3	51	71	147	1,022	−16	−14	−2	5	202
22	M	13	5	52¼	63	155	—	−8				
		13	6	51½	64	151	1,049	−11	−6	−3	3	191
23	F	18	0	54	104	151	—	−9				
		18	3	54	102	150	1,042	−9	−22	−4	3	140
24	F	26	2	54½	101½	157	1,091	−2	(−18)	(−1)	3	268, 254
25	F	29	5	59½	100½	164	1,139	−4	(−14)	(−13)	4	234

* Parentheses are used to set off the Talbot figures if the patients are adults, because the Talbot standards are for children

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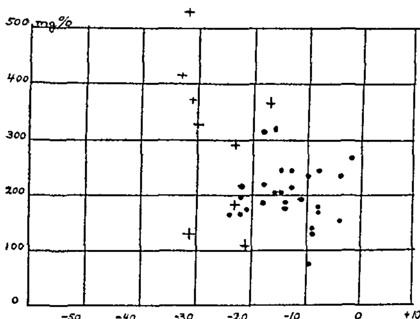


Fig 76—Blood serum cholesterol in mongolism (black dots) and cretinism (crosses) and their relation to basal metabolic rates The average serum cholesterol level in mongolism is between 180 and 280, with some values between 110 and 180 and a few values above 300 The metabolic rate is on the minus side, the majority of cases between —10 and —20, with several values between 0 and —10 and a few values below —20 The cholesterol values in cretinism are usually above 300, but the figure shows that three values in cretin babies were between 100 and 200 The metabolic rate in cretinism is below —20, with the majority of cases below —30, but there is a definite overlapping in the cholesterol values and the metabolic rates between mongolism and cretinism

ranged from —11 per cent through —15 per cent, and 9 were below —15 per cent. The calculations based on the Talbot standards for children gave different results With use of the weight standards, 4 of the rates were on the plus side, and only 4 were below —15 per cent (excuding subject 24, an adult) When the Talbot height standards were used, all rates except 1 (—17 per cent) came into normal range In contrast, all calculations for 3 typical cretins, interpolated because of the patients' small statures, were below normal limits, whether based on Mayo Foundation standards, on Talbot weight and Talbot height standards (although 2 subjects were adults) or on Harris-Benedict standards

Pennacchietti, who advanced the theory of hyperthyroidism in mongolism, has reported a few metabolic rates which do not support his view. Although his results are on the plus side, all are within acceptable normal limits, especially if one considers the difficulty of attaining a so-called basal condition in young children. Calculations

from his data give a percentage of +10, +10, +14, +10, +8, and +17, respectively. In contrast to Pennacchietti's values, our values were all on the minus side

Brain Metabolism

Very little emphasis has been placed on brain metabolism Unfortunately, no histochemical studies of the brain tissue have come to my attention Himwich et al. reported that a constant supply of energy, obtained from oxidation of various foodstuffs, must be available if an organ is to function properly. In contrast to some body tissues like muscle which can oxidize fat when carbohydrate is not available, cerebral metabolism depends entirely on carbohydrates as its foodstuff. The brain can no longer carry on when deprived of this single source of energy, and coma is apt to set in. The brain removes large amounts of carbohydrates from each circulation—estimated to be about 14 6 mg per cent for human subjects. Since there is but little reserve at its disposal, it depends directly on the blood stream for its constant food supply The oxygen consumption of the adult human brain is 7 43 vol per cent. Experiments with insulin shock therapy emphasize the fact that anoxia and hypoglycemia exercise the same effect in depressing brain metabolism Low blood sugar acts, therefore, like anoxia on the central nervous system.

Himwich and co-workers studied the cerebral metabolism in 65 mongoloid individuals In the first communication they reported a reduced consumption in mongoloid infants and adults. However, later studies threw doubt on the validity of these observations At present no reliable studies of brain metabolism in mongolism are available, nor have any studies of the tissue chemistry of the mongoloid system been carried out.

The situation is greatly complicated by the fact that children with congenital heart defects often show cerebral anomalies due to anomalies of circulation. Many mongoloids have a fast pulse rate and a very thin narrow vascular tree This creates differences in rates of circulation and absorption which are not yet fully understood.

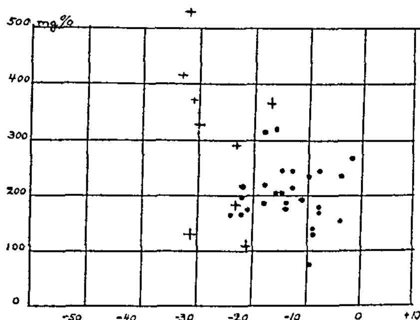


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Pennacchietti, who advanced the theory of hyperthyroidism in mongolism, has reported a few metabolic rates which do not support his view. Although his results are on the plus side, all are within acceptable normal limits, especially if one considers the difficulty of attaining a so-called basal condition in young children. Calculations

on, with the result that the brain shows not only some developmental anomalies but a severe lack of maturation of the nerve cells and of myelination Yet it is not these organs alone that are at fault: every system of ectodermal, mesodermal and endodermal origin shows the same underdevelopment

Hence the conclusion is offered that not the organ systems but the cellular composition of the organism is inhibited in development and function. In mongolism we deal with a general cellular pathology which prohibits proper functioning of the organism and prevents the child afflicted with this condition from reaching full maturity in the prenatal period or ever afterwards

Before discussing the possible explanations for such a deep seated disorder, we may consider figure 3 (page 10), which pictures the prenatal development of a mongoloid child compared with the normal. As may be seen, the mongoloid child goes through a fairly normal "organogenetic" period in the first weeks of fetal development, and then (at about 4 to 5 weeks) developmental deceleration of increasing severity takes place, remaining noticeable throughout life. The anomalies of the heart, brain, bones, dentition—to mention only a few—can be traced back to the second month of fetal development, when they first became apparent.

Most physicians and investigators who discuss mongolism emphasize only its negative aspects and its many anomalies, but it is also important to realize that the child with mongolism is normal in many respects* Why is it that so few obstetricians are able to make a diagnosis of mongolism at the time of delivery of a mongoloid child? Why are only a few well-trained general practitioners or specialists able to recognize mongolism before its manifestations become more apparent—often several years after birth? Obviously [illegible] cause th[illegible]

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[illegible]

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CHAPTER IX

ETIOLOGY

THE PROBLEM OF GENETIC FACTORS

The etiology or causation of mongolism has been a matter of much debate since 1866, when Langdon Down wrote his classic description of the condition. Every explanation emphasizes a different aspect of the disorder, resulting in many different constructs of etiology. This spectrum of opinion implies a failure to first establish what mongolism actually represents. We cannot expect to find the etiologic factors before we know the type of pathology underlying the abnormal condition. Are we dealing with an organ deficiency, as in cretinism, in which the pathology is due to aberrations of thyroid structure and function? Are we dealing with a metabolic process, as in phenylpyruvic oligophrenia or the amaurotic idiocies, in which certain errors in metabolism are the cause? Or are we dealing with a malformation of a specific nature, as in cleft formations, myelomeningoceles, or other developmental disorders of the central nervous system? Answers to these questions had to be found before a successful search for the etiology of mongolism could be undertaken.

Our research over the last 25 years has established beyond doubt *that mongolism is a prenatal growth deficiency in which central* growth regulation is at fault. The child with mongolism suffers from a deceleration of growth during the prenatal period which results in a highly complex, multidimensional disorder in which every organ is involved. In our extensive studies of organ pathology, we have been able to demonstrate that in the postnatal period the endocrine organs are at fault, with resultant anomalies in pituitary, thyroid, adrenal, gonadal and liver function. We have shown that the accumulation of eosinophilic cells in the pituitary, so often seen in this condition, is apparently due to an accumulation of growth, thyrotropic and adrenotropic hormones which cannot be properly discharged because the target organs do not respond adequately. At the same time we have established that faulty pituitary function is apparently due to the severe *developmental disorder of the central nervous system*, which exhibits failure of proper development from early embryonic stages

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certain conditions: (a) Unless we deal with a sex-linked recessive gene, paternal and maternal factors are of equal importance. (b) Although not every child is affected, the more numerous the offspring, the more likely that more than one child will be affected. (c) In hereditary disorders due to recessive genes, consanguinity between parents is found more frequently than in the control population. (d) Of twins, monozygotic twins are always concordant, dizygotic twins either discordant or concordant according to the penetrance of the recessive gene

Needless to say, studies of several thousands of families in which a mongoloid child has been born have provided conclusive evidence that hereditary-genetic factors can be excluded in mongolism. Although a second mongoloid is occasionally observed in a family (about one instance in 100 families with mongolism) and a few families are known to have three mongoloid children, the constellation of such multiple occurrences is so rare and so different from other hereditary-genetic disorders that another interpretation must be sought for these cases

The available material is so conclusive that it is no longer necessary to discuss hereditary-genetic factors. Even Penrose states that "The reasons for rejecting any simple Mendelian explanation, as envisaged by Macklin (1919) are evident."

Gene mutations occur occasionally, creating individual abnormalities It is not likely, however, that a ... occur with ... concordant ... which diss... twins, male and female, are affected), the explanation of a spontaneous mutation is far-fetched As Jervis points out:

> If exclusively chromosomal factors are operating, the proportion of concordant dizygotic twins to discordant dizygotic twins should be reasonably close to the proportion of sibships with two members affected to sibships with only one member affected Although reliable data concerning the incidence of familial mongolism are scanty, one may reasonably assume that no more, and probably less than 1 per cent of affected sibships show more than 1 mongoloid The proportion of concordant dizygotic twins to discordant dizygotic twins is 6 8 per cent or 7 times, and probably more, the incidence of familial mongolism This discrepancy appears significant It would suggest that other than genetic factors are present

Twin research has been the main instrument of genetic research in recent decades, and indeed many genetic questions have been decided only through adequate investigations in twinning. Unfortunately, in spite of a large number of reports on mongoloid twins, the observations are inconclusive in many respects.

the anomaly must be sought at the same time. Actually we have to assume that something had happened to the organism before the onset of the abnormal manifestations, and it is quite possible that deceleration of growth at that time occurs because of cellular defects which can be traced back to the time of fertilization or even before.

For an understanding of such a deep-seated cytoplasmic disorder, four main theories have been advanced: (a) hereditary-genetic, (b) spontaneous gene mutation, (c) fertilization of an "over-aged" ovum, and (d) extrinsic environmental factors interfering with fetal development. To clarify the situation, a more adequate etiologic evaluation may be presented in the following:

Period of damage	*Effect*
1 Preconceptual	Genetic disorder anomalies of gene function— (a) hereditary, (b) spontaneous mutation
2 Time of conception	Zygotic disorder anomalies of fertilized ovum—(a) chromosomal, (b) cytoplasmic
3. Gestation	Developmental disorder anomalies of developing fetus—(a) nutritional; (b) infectious, (c) anoxemic, (d) others

As may be seen, genetic disorders (anomalies of genes) may be due to two different causes: the transmission of abnormal genes from ancestors (hereditary disorders) or the mutation of genes which occurs for the first time in the afflicted individual. Genes are unit *processes* or unit determiners, rather than unit characters. In chemical terms, a gene is considered a nucleoprotein, probably a molecule or even less. Its action is a specific oxidation or catalyzing process, similar to the action of enzymes or viruses. It is quite possible that enzymes, now better understood as the most fundamental catalyzing agents, are represented by genes These fundamental enzymatic actions which determine the specific development of an organism are transmitted through genes, linked together in a chromosomal molecule. There are genes postulated for practically every biologic unit-action. In a series of brilliant investigations, genetic scientists have demonstrated that genes are side chains on the chromosomes. The chromosomal bands are formed from the chromatin of the nucleus when the cell or gamete (sperm or ovum) undergoes cell cleavage.

It is unfortunate that investigators who discuss gene anomalies do not distinguish clearly between hereditary disorders and gene mutation, and often imply that any gene anomaly must be due to hereditary transmission. Thus it has been suggested by a number of investigators that mongolism is due to a recessive gene.

Hereditary disorders due to recessive genes become manifest under

prisingly, they found that the normal co-twins were more normal or less stigmatized than is claimed for younger siblings of mongoloid patients I have always questioned the significance of these abortive expressions of mongolism, which are supposed to suggest some embryonic vulnerability. The study of normal co-twins does not favor such interpretation, but it also seems to suggest that the adverse environmental factors which produce one mongoloid child are not general enough to impair the development of the co-twin. If peristatic factors are involved, they must be related to the affected child and his immediate environment during the time of gestation.

Of the many publications on twin pairs in which one or two children are affected, the publications of Allen, Baroff and Kallmann are of special interest since they deal with 33 well studied twin pairs in institutions of the State of New York in which all twins among the retardates have been reported The study shows that mongolism does not occur more frequently among twins Actually, among the total admissions to New York State Schools there were 2 59 per cent twins among the undifferentiated and familial cases while only 1.95 per cent were found among the mongoloids. This frequency is in contrast to the much higher percentage of twinning in the cerebral palsy group (3 86 per cent) and the post-traumatic (birth injuries) group, in which 5 02 per cent were found.

Considering the conditions under which twin pregnancies occur, the environmental factors in twins are often quite different. Not only do the places of implantation differ (one ovum may find a "place in the sun" while the other is pushed aside [fig 77]), but the formation of the embryonic mantle is greatly influenced by conditions created by the favorably placed ovum There is evidence that twin pregnancies occur under many different conditions. Nonidentical twins may be due to two ova, released at the same time from the same ovum but two graafian follicles, or from the same follicle, or even from two ova in the same germ center But they may also be due to ova released from two ovaries, and may even be fertilized on different occasions The arrival of the two fertilized ova in the uterine cavity may differ by several days, and the second ovum may find the uterine mucosa in a state of reaction to the first ovum and entirely unfavorable to a new nidation

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Twins, in the human species, are considered to come from two sources The first group occurs as the result of the complete cleavage of one fertilized ovum and the development of two separate individuals. This type of twinning is called "enzygotic" or "monozygotic," because the twins have developed from one zygote or fertilized ovum. Other terms that are used are "uniovular," "similar," and "identical." These twins are always of the same sex and show identical color of hair and of eyes, the same blood groups, the same patterns of the hand lines, and many other minor details In the vast majority of cases they develop from one placenta and have the same fetal membranes The second type of twins is produced through fertilization of two ova at the same time, both ova coming either from the same ovary or from separate ovaries These twins are called "dizygotic," arising from two zygotes They are also called "binovular," "dissimilar," and "fraternal." These twins, who happen to be born at the same time, resemble each other as much or as little as any pair of siblings do They may be of the same or of the opposite sex They will differ in many ways and may have no more in common with each other than any two children of the same parents

In a group of 90 pairs of twins, 60 may be expected to be of one sex and 30 of opposite sex The twin pairs of opposite sex are undoubtedly dizygotic. The remaining 60 pairs of twins of one sex have to be divided into monozygotic and dizygotic According to estimates, one-half of these 60 pairs are likely to be dizygotic and one-half monozygotic *

If a pathological condition is found in both twins, the condition is called "concordant" If the condition is present in only one, it is called "discordant"

It is impossible to determine exactly how many observations on mongoloid twins have been reported. Øster states that "97 instances of mongolism in one (79) or both (18) twins have been described in the literature" (page 126) However, not all these cases were thoroughly analyzed. The results of all observations can be summarized in the statement that all pairs of monozygotic twins have been found concordant; but two definite cases are known in which twins of different sex, and therefore dizygotic twins, have been concordant, and there are a number of other concordant twin pairs (at least six) in whom dizygoticity is recognized by the genetic experts.

Thus, as mentioned before, the observations are against a theory of spontaneous mutation and favor a zygotic deficiency or adverse factors at the time of the earliest cleavages. In this respect, another aspect of twinning which seems of great interest has been discussed extensively by Gordon Allen and George Baroff: "When only one member of a twin pair is mongoloid, does the co-twin carry any stigmata that can be attributed to the same cause as his partner's mongolism?" Sur-

* Of course, the actual distribution in a population differs from this theoretical number Since twinning also increases with advanced age of the mother, [illegible] nd Baroff, [illegible] per cent

been reported in which the father had been exposed to some damage to his progenitive system (testicular tumors, radiation damage or others) Some of these cases cannot withstand critical analysis, and others do not exclude mere coincidence. On the other hand, certain characteristics in the mother repeat themselves with such frequency that they must be considered of definite significance.

A series of investigations which culminated in a study by Adrian Bleyer, based on the material of 2822 cases in 1928, gives evidence that the age of the mother plays an important role in mongolism. The average age of the mother at the time of the birth of a mongoloid child was found to be more than 10 years higher than the average maternal age at the time of birth of two million children who were born in the United States in 1934. More than 50 per cent of mothers were beyond the age of 35 when their mongoloid child was born. Figure 78 shows the age of 255 mothers of mongoloid children of the Wrentham material This chart confirms earlier observations that

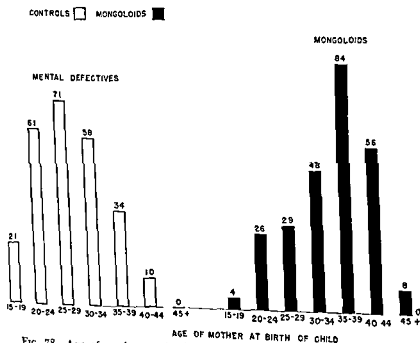


FIG 78—Age of mothers at birth of mongoloid child In a control series of 255 cases, the age distribution of the mothers corresponds to the normal distribution with the largest number of children born between the ages of 25 and 29 years The largest number of mongoloids are born to mothers between 35 and 39 years of age The age difference between the two groups is almost 10 years

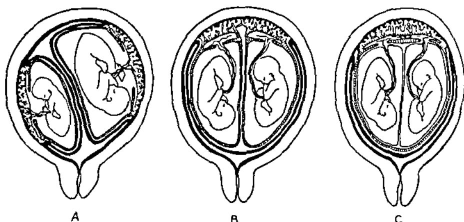


FIG 77—Three forms of twin pregnancies, demonstrating possible differences in position and nutritional environment (*A*) Twins with two placentas and two entirely different amniotic sacs The right twin has a favorable nidation in the upper segment of the uterus and can be born by normal delivery The nidation of the left twin is near the orifice and may lead to placenta praevia The left twin may be born by breech presentation He may be much smaller than the right twin, compressed and damaged, and may develop cerebral palsy or other anomalies (*B*) Twin pair with one placenta but two different sacs and separate nutritional supplies The right twin will be born by breech presentation because version is unlikely One of the twins may grow better and be considerably better developed than the other twin. (*C*) Fraternal twins with one placenta and one amniotic sac. However, nutritional conditions can vary to a great extent even in this pair

antigen M and the other MN The father's blood showed the group AB and factor N *Experiments and testings, carried out independently by three experts* provided scientific proof that the alleged father could not be the father of one of the twins and that, therefore, superfecundation, or impregnation of a second ovum matured in the same ovulation cycle, can exist in humans [Heberer]

PRENATAL MATERNAL FACTORS

While a hereditary-genetic disorder and a spontaneous gene mutation can be excluded as causes of mongolism, we and other investigators have accumulated a wealth of material which indicates that the condition of the mother—either at the time of conception or shortly thereafter—is responsible for the occurrence. Which moment in the development of a child is more suspect shall be discussed in the third section. At this point we will present certain characteristics of the material in more detail.

It may be mentioned briefly that a study of the two variables in the etiology of a mongoloid child—the paternal and maternal germ plasm—indicates that no consistent anomalies on the part of the father have ever been found, although single cases have occasionally

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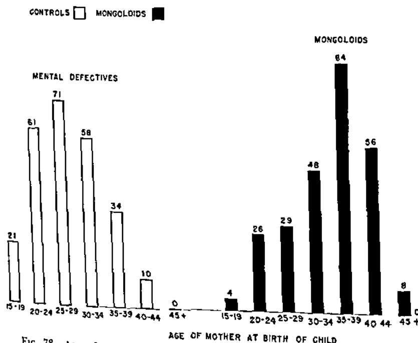


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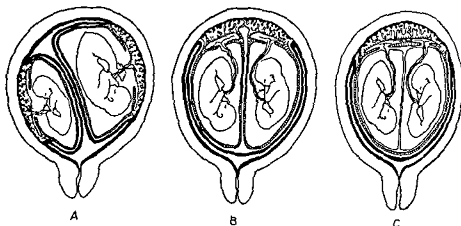


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TABLE 24.—*Order of Birth in 4,316 Mentally Defective Public School Children*
Analysis Confined to Families with One to Nine Children
(Dayton)

Order of birth of ment def child	Size of family									Total
	1	2	3	4	5	6	7	8	9	
1	209	193	190	156	149	119	77	40	16	1,149
2	—	175	146	141	154	123	85	56	38	918
3	—	—	133	144	137	107	88	72	44	725
4	—	—	—	117	109	93	91	76	61	547
5	—	—	—	—	98	80	84	67	52	381
6	—	—	—	—	—	96	82	68	43	289
7	—	—	—	—	—	—	70	50	44	170
8	—	—	—	—	—	—	—	58	37	95
9	—	—	—	—	—	—	—	—	42	42
Total	209	368	469	558	647	618	577	493	377	4,316

TABLE 25.—*Siblings Born Before and Subsequent to Birth of Mentally Defective Child, by Size of Family*

Size of family	Total siblings born	Siblings born before patient	Patient affected	Siblings born after patient
1	209	0	209	0
2	736	175	368	193
3	1,407	412	469	526
4	2,232	780	558	894
5	3,235	1,147	647	1,441
6	3,708	1,416	618	1,674
7	4,039	1,700	577	1,762
8	3,944	1,778	493	1,673
9	3,393	1,591	377	1,425
Total	22,903	8,999	4,316	9,588
Per cent	100	39 2	18 8	41 8

Table 25 shows the number of siblings born before and after the mentally deficient child by size of family. We note that 8999 children, or 39 2 per cent, were born before the mentally defective child and 9588, or 41.8 per cent, afterwards This is very close to the expectation Mental defect as a characteristic does not appear to be associated with any particular disturbance of the birth order.

In order to provide further material for direct comparison, we studied the order of birth of 255 feeble-minded children in the Wrentham State School All had been diagnosed as familial mental defect. Count-

many mongoloid children are born to mothers beyond the age of 35 Instead of a comparison of the material with normal children, a comparison with the ages of mothers at birth of mentally defective children of another type was made. These cases had been diagnosed as familial or germ plasm defect. The differences between the two groups were striking. Most of the mothers of familial mentally defective children were below the age of 30 and only 3 per cent were over 40 years. In the mongoloid group 27 per cent of the mothers were over 40 years.

Age, however, cannot be the only factor in producing mongolism, because 107 of the 255 mothers in this group were under 35 years of age. Thus, about 41 per cent of the mothers were in an age group (under 35) which is favorable for childbearing. Although a maternal age of over 35 years may favor the occurrence of a mongoloid child, it is clear that the factors which produce mongolism are not invariably linked with age.

Birth Order

Whether the condition of the mother or a gametic factor is responsible for mongolism may be answered by a study of the birth order of the mongoloid child.

The birth of a mentally defective child in which the defect is due to germinal deficiency may be expected to occur at any place in the line of siblings It is well known that defectives of the familial type occur as first children, in the middle of the family or as last children Apparently the birth of the mental defective has no influence upon the ability of the mother to have more children Here we are dealing with a problem of genetics and expect no disturbance of the birth order. (On the other hand, if a pathologic condition of the mother were the cause of a defect, we would expect a difference between the number of siblings born before and the number born after the affected child) In some families, the affected sibling may be born first, in other families last. However, these differences will cancel each other in the long run, and the findings will show a balance of siblings born before and after the affected child.

As Dayton has shown previously in a study of birth order in 4316 mentally defective children of all types, there is no evidence that the mentally defective child tends to be born in the first or in the last position of the family. Taken as a whole, the trait of a mental deficiency occurs with almost equal frequency at any place in the birth order The material confined to the birth order of the first 9 children is presented in table 24.

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5	—	—	—	—	98	80	84	67	52	381
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TABLE 26.—*Siblings Occurring Before and After the Mongoloid Birth*

	Mongoloids	Siblings born before mongoloid	Siblings born after mongoloid	Total
Benda				
Expected	255 (21 6%)	462 (39.1%)	462 (39 1%)	1,179 100%
Observed	255 (21 6%)	776 (65 8%)	148 (12 5%)	1,179 100%
Lahdensuu				
Expected	174 (23 9%)	276 (38 0%)	276 (38 0%)	726 100%
Observed	174 (23 9%)	480 (66 1%)	72 (9 9%)	726 100%

TABLE 27.—*Siblings Occurring Before and After the Control (Control Defectives)*

	Control mental defectives	Siblings born before control	Siblings born after control	Total
Benda				
Expected	255 (17 2%)	609 5 (41 3%)	609 5 (41 3%)	1,474 100%
Observed	255 (17 2%)	655 (44 4%)	564 (38 2%)	1,474 100%
Dayton				
Expected	4,316 (18.8%)	9,293 (40 5%)	9,293 (40 5%)	22,903 100%
Observed	4,316 (18 8%)	8,999 (39 2%)	9,588 (41 8%)	22,903 100%

ing the whole number of siblings of the defective child, 54 per cent were born previously and 46 per cent were born subsequently to the patient. This represents a variation which is well within the expected variation and offers, again, proof of the theoretical assumption

Figure 80 represents the situation in mongoloid families by age of mother. Since the number of cases is identical in figures 79 and 80, immediate comparison is possible. The first column shows the mongoloid as the first child of young mothers, aged 15 to 19 years. The striking item in this age group is the small number of siblings who were born afterwards. Only 9 children were born after the mongoloid as compared with 50 siblings born after the mental defective (control material). In the age group 20 to 24 years, the number of children born afterwards is larger than that of siblings born before, but only a total of 32 children is born from 26 mothers in that age group In the age group 25 to 29 years the reversal of the birth order is already present, while the control group shows the theoretical balance between those born before and afterwards In the mongoloid group, the 29 mothers aged 25 to 29 years had only 25 children afterwards, or less than half of the number born before (52). Most striking is the unexpected drop of children born afterwards in mothers aged 30 to 34 years, among whom only 29 children appeared, as compared with 117 born afterwards in the control group.

One point is worth noticing. In families with a mongoloid child, the number of normal previously born siblings from mothers between the ages of 30 and 34 is very small, while in the age groups of 35 to 39 and 40 to 44, the number of normal siblings is much larger than in the controls. This seems to indicate that in families with a mongoloid child at the end of the childbearing period, the age of the mother at the time when their normal children were born was higher than in other families In other words, these mothers have started childbearing at a higher age than had those of the control group

If mongolism were a genetic disorder, we would expect a random occurrence in the birth order, which statistically would result in half the normal children being born prior to the mongoloid, and half after the mongoloid In comparing the number of siblings born before and after a mongoloid child, the striking result is found that 81 per cent of the total number of brothers and sisters (100 per cent) are

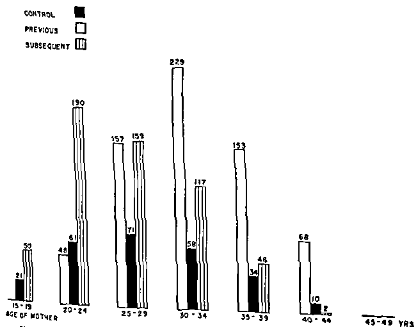


Fig 79 —Number of siblings born previous and subsequent to control birth. In the age group between 25 and 29 years almost exactly as many siblings are born after the defective child as before In the age group 20 to 24 years the number of siblings born after a defective child is four times that of siblings born before, indicating that the birth of a hereditarily defective child has no influence upon the birth rate afterwards In the age group 30 to 34 years about half as many children are born after a defective as before

TABLE 26.—*Siblings Occurring Before and After the Mongoloid Birth*

	Mongoloids	Siblings born before mongoloid	Siblings born after mongoloid	Total
Benda				
Expected	255 (21.6%)	462 (39.1%)	462 (39.1%)	1,179 100%
Observed	255 (21.6%)	776 (65.8%)	148 (12.5%)	1,179 100%
Lahdensuu				
Expected	174 (23.9%)	276 (38.0%)	276 (38.0%)	726 100%
Observed	174 (23.9%)	480 (66.1%)	72 (9.9%)	726 100%

TABLE 27.—*Siblings Occurring Before and After the Control (Control Defectives)*

	Control mental defectives	Siblings born before control	Siblings born after control	Total
Benda				
Expected	255 (17.2%)	609.5 (41.3%)	609.5 (41.3%)	1,474 100%
Observed	255 (17.2%)	655 (44.4%)	564 (38.2%)	1,474 100%
Dayton				
Expected	4,316 (18.8%)	9,293 (40.5%)	9,293 (40.5%)	22,903 100%
Observed	4,316 (18.8%)	8,999 (39.2%)	9,588 (41.8%)	22,903 100%

ing the whole number of siblings of the defective child, 54 per cent were born previously and 46 per cent were born subsequently to the patient. This represents a variation which is well within the expected variation and offers, again, proof of the theoretical assumption.

Figure 80 represents the situation in mongoloid families by age of mother. Since the number of cases is identical in figures 79 and 80, immediate comparison is possible. The first column shows the mongoloid as the first child of young mothers, aged 15 to 19 years. The striking item in this age group is the small number of siblings who were born afterwards. Only 9 children were born after the mongoloid as compared with 50 siblings born after the mental defective (control material). In the age group 20 to 24 years, the number of children born afterwards is larger than that of siblings born before, but only a total of 32 children is born from 26 mothers in that age group. In the age group 25 to 29 years the reversal of the birth order is already present, while the control group shows the theoretical balance between those born before and afterwards. In the mongoloid group, the 29 mothers aged 25 to 29 years had only 25 children afterwards, or less than half of the number born before (52). Most striking is the unexpected drop of children born afterwards in mothers aged 30 to 34 years, among whom only 29 children appeared, as compared with 117 born afterwards in the control group.

average The imbalance between the number of children born before and afterwards suggests that the birth of a mongoloid child marks the development of a pathologic condition of the mother which bears a definite relationship to her ability to have children. The decrease in fecundity of the mother after a mongoloid child is not complete, as a small number of children are born afterwards. The condition of the mother is not irreversible; and yet, the material shows that the birth of a mongoloid child marks a turning point which is followed by a decided diminution in the number of children born subsequently.

In table 28 the birth order of mongoloid children is presented. In order to show that the peculiarities of the birth order are not confined to the Wrentham material, material from a recent publication of Sa-

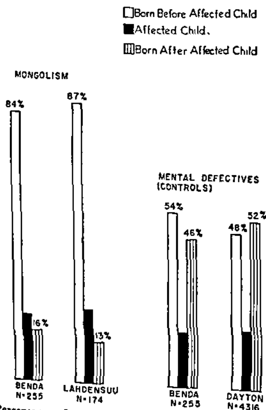


Fig 81 —Percentages of sibl[illegible] and mongoloids. If the [illegible] fective child are compa[illegible] while in the mongoloid [illegible] of all siblings are born before the mongoloid and only 13 to 16 per cent after the mongoloid.

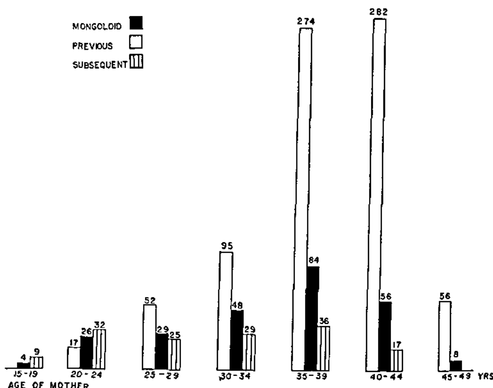


FIG. 80 —Number of siblings born previous and subsequent to mongoloid birth In the age group 25 to 29 years only half as many children are born after the mongoloid as before, instead of the same number, and in the age group 20 to 24 years less than twice as many children are born after a mongoloid as before, instead of four times as many.

born before the mongoloid child and only 16 per cent are born afterwards. In a total of 1179 siblings, 255 were mongoloids We might have expected 462 children to be born *before* the mongoloids and 462 born *afterward* Instead, we find that 776 children were born before the mongoloid and only 148 afterward Only 12.5 per cent of the siblings were born after the mongoloid when we might have expected 39.2 per cent.

The total number of siblings born in 255 families with mongoloid children is 924, which is only slightly less than the control group with 1,219. In the mongoloid group, the total number of children born before the defective child is 776, while in the control group 655 children were born before. In other words, mothers who later gave birth to a *mongoloid* child had a period in their lives when they bore children at the average rate for all mothers or even above. Then something happened: As a result, a mongoloid was born, and from that point on these mothers produced at a rate which was much below the

TABLE 28 —*Order of Birth in 255 Mongoloids at the Wrentham State School Compared with Data of Lahdensuu (174 Cases)*

WRENTHAM STATE SCHOOL

Order of birth of mongoloid	No of children born in family															Total no of mongoloids
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
1	20	12	8	1	3	—	—	—	—	—	—	—	—	—	—	44
2	—	40	9	4	1	—	—	1	—	—	—	—	—	—	—	55
3	—	—	33	9	4	2	1	—	—	—	—	—	—	—	—	49
4	—	—	—	20	5	1	—	—	—	—	—	—	—	—	—	26
5	—	—	—	—	11	4	—	—	—	—	—	—	—	—	—	15
6	—	—	—	—	—	7	5	1	—	—	—	—	—	—	—	13
7	—	—	—	—	—	—	7	5	—	1	—	—	—	—	—	13
8	—	—	—	—	—	—	—	5	6	1	1	—	—	1	—	14
9	—	—	—	—	—	—	—	—	6	3	—	—	—	—	—	9
10	—	—	—	—	—	—	—	—	—	5	—	1	—	—	—	6
11	—	—	—	—	—	—	—	—	—	—	5	1	1	—	—	7
12	—	—	—	—	—	—	—	—	—	—	—	1	1	—	—	2
13	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	1
14	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1
	20	104	150	136	120	84	91	96	108	100	66	36	39	14	15	255

Total children born in these families, 1,179

SAKARI LAHDENSUU

Order of birth of mongoloid	No of children born in family													Total no of mongoloids
	1	2	3	4	5	6	7	8	9	10	11	12	13	
1	36	11	2	1	1	—	—	—	—	—	—	—	—	51
2	—	18	4	1	2	1	—	—	—	—	—	—	—	26
3	—	—	14	3	2	—	—	1	—	—	—	—	—	20
4	—	—	—	20	—	2	—	—	—	—	—	—	—	22
5	—	—	—	—	9	—	—	1	—	—	—	—	—	10
6	—	—	—	—	—	8	1	1	1	—	—	—	—	11
7	—	—	—	—	—	—	12	2	1	1	—	—	—	16
8	—	—	—	—	—	—	—	5	—	—	—	—	—	5
9	—	—	—	—	—	—	—	—	4	—	—	—	—	4
10	—	—	—	—	—	—	—	—	—	2	1	—	—	3
11	—	—	—	—	—	—	—	—	—	—	3	1	—	4
12	—	—	—	—	—	—	—	—	—	—	—	1	—	1
13	—	—	—	—	—	—	—	—	—	—	—	—	1	1
	36	58	60	100	70	66	91	80	54	30	44	24	13	174

Total children born, 726

kari Lahdensuu is added. Both charts show identical trends. There is a definite difference between the families in which the mongoloid is among the first 5 children and those in which the mongoloid is born in a family of more than 6. In contrast to table 24, in which mentally deficient children appear on any place of birth order, the mongoloid child never occurred among the first children in those families who had 6 to 15 siblings. The larger the family, the more definite the trend toward the end of the birth line. Not in every case is the mongoloid child exactly the last child, but in those families with more than 5 children the mongoloid is almost always among the last 3 children. We recorded in our list all pregnancies resulting in a living child. It may be mentioned that a study of the siblings revealed that in a rather large number of cases, the siblings born after a mongoloid died shortly after birth. Many more mongoloids are, therefore, the last living child than appear in that position on our table. In these families, the siblings born before the mongoloid appear normal. The mothers of these families have revealed no pathology in their younger years and have offered evidence of their ability to give birth to a rather large number of normal children. In each case, the pathology in the offspring occurred only as the mother was approaching the end of her childbearing period or had reached the condition in which menstruation had become irregular.

I mentioned that the ages at which the normal pregnancies occurred seem to be important. From the tables one learns that many of the normal siblings were born after the mother was 30 years of age; the 6 to 15 pregnancies which some of these mothers had were not spread over a period of 10 to 20 years but were sometimes found crowded into a rather short period after the maternal age of 30 Obviously, bearing a given number of children after 30 represents a heavier strain on the organism of the mother than having the same number of children at a younger age does The observation on this group of families seems to confirm the theory of Shuttleworth, who called the mongoloid child an "exhaustion product," the occurrence of which is "dependent upon conditions adversely affecting the maternal reproductive powers, the advanced age of the mothers and the frequent childbearing being the most noticeable causative factors—exhaustion, illness of whatever kind during the period of gestation may produce imperfection in the evolution of the foetus and its tissues which we know as mongolism."

Age and exhaustion, however, cannot be the only factors, because we find in our other group that a large number of mongoloids are the first children in the family and that the total number of children in

TABLE 28—*Order of Birth in 255 Mongoloids at the Wrentham State School Compared with Data of Lahdensuu (174 Cases)*

WRENTHAM STATE SCHOOL

Order of birth of mongoloid	No of children born in family															Total no of mongoloids
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
1	20	12	8	1	3	—	—	—	—	—	—	—	—	—	—	44
2	—	40	9	4	1	—	—	1	—	—	—	—	—	—	—	55
3	—	—	33	9	4	2	1	—	—	—	—	—	—	—	—	49
4	—	—	—	20	5	1	—	—	—	—	—	—	—	—	—	26
5	—	—	—	—	11	4	—	—	—	—	—	—	—	—	—	15
6	—	—	—	—	—	7	5	1	—	—	—	—	—	—	—	13
7	—	—	—	—	—	—	7	5	—	1	—	—	—	—	—	13
8	—	—	—	—	—	—	—	5	6	1	1	—	—	1	—	14
9	—	—	—	—	—	—	—	—	6	3	—	—	—	—	—	9
10	—	—	—	—	—	—	—	—	—	5	—	1	—	—	—	6
11	—	—	—	—	—	—	—	—	—	—	5	1	1	—	—	7
12	—	—	—	—	—	—	—	—	—	—	—	1	1	—	—	2
13	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	1
14	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1
	20	104	150	136	120	84	91	96	108	100	66	36	39	14	15	255

Total children born in these families, 1,179

SAKARI LAHDENSUU

Order of birth of mongoloid	No of children born in family													Total no of mongoloids
	1	2	3	4	5	6	7	8	9	10	11	12	13	
1	36	11	2	1	1	—	—	—	—	—	—	—	—	51
2	—	18	4	1	2	1	—	—	—	—	—	—	—	26
3	—	—	14	3	2	—	—	1	—	—	—	—	—	20
4	—	—	—	20	—	2	—	—	—	—	—	—	—	22
5	—	—	—	—	9	—	—	1	—	—	—	—	—	10
6	—	—	—	—	—	8	1	1	1	—	—	—	—	11
7	—	—	—	—	—	—	12	2	1	1	—	—	—	16
8	—	—	—	—	—	—	—	5	—	—	—	—	—	5
9	—	—	—	—	—	—	—	—	4	—	—	—	—	4
10	—	—	—	—	—	—	—	—	—	2	1	—	—	3
11	—	—	—	—	—	—	—	—	—	—	3	1	—	4
12	—	—	—	—	—	—	—	—	—	—	—	1	—	1
13	—	—	—	—	—	—	—	—	—	—	—	—	1	1
	36	58	60	100	70	66	91	80	54	30	44	24	13	174

Total children born, 726

these families is rather small. If one investigates the correlation between the age of the mother and the number of children one finds that mongoloids occur mainly under two conditions Of those 8 mothers who were above 45, all had more than 3 children, with a total of 56 children. Among 56 mothers between 40 and 44, 40 had more than 3 children, totaling 264 children, but in 5 instances the mongoloid was the result of the first pregnancy. In the age group between 35 and 39, we find 84 mothers, of whom 43 had more than 3 children, totaling 228 children, while 9 in that group had no child before. One may therefore conclude that the risk of childbearing at an age beyond 35 is increased in any case, regardless of whether many pregnancies or no pregnancy had occurred before. In the latter instance, the maternal organism has apparently lost its adaptability for pregnancy. In the age group of 20 to 24, we find 26 mothers of whom 14 had a mongoloid as their first child, but 2 women had already given birth to a total of 7 children; in the age group of 25 to 29, 4 mothers had no children before the mongoloid but 6 had borne a total of 23 children before.

TABLE 29 —*Correlation between Age of Mother and Number of Pregnancies*

Age group of mother	No of mothers	No child	1 child	2 children	3 or more children	Total no of children
			BEFORE MONGOLOID BIRTHS			
15–19	4	4	0	0	0 (0 children)	0
20–24	26	14	10	0	2 (7 ")	17
25–29	29	4	9	10	6 (23 ")	52
30–34	48	8	14	18	9 (45 ")	95
35–39	84	9	18	14	43 (228 ")	274
40–44	56	5	4	7	40 (264 ")	282
45–49	8	0	0	0	8 (56 ")	56
Total	255	44	55	49	108 (623 ")	776
			AFTER MONGOLOID BIRTHS			
15–19	4	1	1	0	2 (8 children)	9
20–24	26	8	9	7	2 (9 ")	32
25–29	29	16	5	5	3 (10 ")	25
30–34	48	31	11	3	3 (12 ")	29
35–39	84	57	21	4	2 (7 ")	36
40–44	56	41	13	2	0 (0 ")	17
45–49	8	8	0	0	0 (0 ")	0
Total	255	162	60	21	12 (46 ")	148

We see that a rapid sequence of pregnancies may produce a temporary condition of unfitness for gestation On the other hand, the first fertilization may occur under physiologic and psychologic conditions which are highly unfavorable for a normal pregnancy If mongolism occurs in the first pregnancy, the mother may well be able to react normally in a second and a third pregnancy.

Psychosomatic Disorders of Mother

In the following I comment briefly on the psychosomatic factors common in mothers who have given birth to a mongoloid child: (1) high-strung, nervous, easily upset personality, (2) frequency of abortions, (3) bleedings during pregnancy; (4) inability to keep a full-term pregnancy (prematurity of baby); (5) inability to become pregnant; and (6) endocrine imbalance

In a study by Bowman and the author in 1953, these investigators examined the psychological factors in 24 mothers who had given birth to a mongoloid child. Six of them were found to be severely disturbed, with depres-

... observed in 15 instances Among the 24 mothers, 20 declared that they had become pregnant against their own wish, and 14 admitted that they were not reconciled with their pregnancy during the whole period of gestation Of the four mothers who insisted that the pregnancy was planned, two were actually very depressed and in psychotherapy at the time of conception.

These observations are in some disagreement with observations mentioned by this author before—that most of the mongoloid children were very much desired.

Abortions

The frequency of abortions is one of the most striking features in case histories of mongolism.

Table 30 shows that 80 of 255 mothers have reported a total of 126 miscarriages ...

tion ...

The

... become available in recent years, the more frequently we have found that the first signal for threatening mongolism was given in a miscarriage

The incidence of spontaneous abortions in the general population

TABLE 30.—*Miscarriages and Stillbirths in 255 Mothers Having a Mongoloid Child*

Age groups	No	No of mothers having miscarriages	No of miscarriages before and after Pt		Total	%
			Before	After		
15–19	4	1	1	0	1	25
20–24	26	5	0	5	5	19 2
25–29	29	7	6	6	12	24
30–34	48	19	21	7	28	39 3
35–39	84	29	42	12	54	29
40–44	56	15	19	1	20	26 9
45–49	8	4	6	0	6	50
Total	*255*	*80*	*95*	*31*	*126*	*31 2*

has attracted much interest on the part of obstetricians and pathologists. In a recent article A. T. Hertig and R. G. Livingstone reviewed this subject and found the incidence to be 10.6 per cent The summarized findings of various authors indicate that 9.8 per cent of all pregnancies terminate in spontaneous abortion. In families in which a mongoloid child is born, the average for the whole group is 31.2 per cent, with variations from 19.2 per cent to 50 per cent, according to age groups This indicates a three times higher rate of spontaneous abortions than in the general population. The material of the Lying-in Hospital, Boston, investigated with regard to mongolism by Beidleman, revealed an incidence of 19 per cent abortions, or twice the number of the control group

The high incidence of abortions has recently led M. Engler to find the "sole cause" of mongolism in a preceding artificial or spontaneous abortion which has caused "*a serious alteration of the mucous membrane of the uterus*" *The implanted ovum finds pathologic* conditions which hamper its nourishment. This is a revival of the old nidation theory, with the modification that not chronic but acute changes in the uterine mucosa are the cause. The incidence of previous abortions (in Engler's own material, 18 9 per cent), however, is far too low to base a theory of faulty nidation on it Moreover, the many normal children born *after a mongoloid make the uterine nidation theory* still less tenable The frequency of abortions is an important clinical symptom, the interpretation of which will be given later.

Bleedings and Threatened Abortion

Probably closely related to the frequent miscarriages is another phenomenon. Many *times the mother has observed a continuation of*

her regular menstruation during the second and third months of the pregnancy that terminated in a mongoloid child. Sometimes bleedings were irregular, or abortion threatened but was prevented through rest. The continuation of menstruation during pregnancy indicates that the endocrine mechanism preventing a uterine bleeding is at fault. The concept of a threatened abortion is not uniform, because some writers consider the occurrence of uterine cramps as a sign of impending abortion. In my study only those cases were recorded in which actual bleedings were observed. The percentage was 14.6. Beidleman found an incidence of 23 per cent in the Boston Lying-in Hospital mongoloid material The figure of threatened abortion is 4 per cent for the same hospital for the general population, according to Rutherford, and 3.8 per cent, according to Paine. Several writers, including Hertig, feel that the percentage is slightly higher in private practice, but even then, a percentage of 14.6 to 23 is again at least three times higher than what one might expect.

Prematurity

Table 31 shows the increased incidence of prematurity in mongolism Of the limited number of cases in which I found a definite birth record, prematurity was recorded 44 times, in contrast to 12 instances of prematurity in our feeble-minded control material Prematurity is very likely a part of the general disorder which results in a mongoloid child

Beidleman found in his material a prematurity incidence of 43 per cent in mongoloid babies, as against 3 2 per cent for all other babies

TABLE 31 —*Birth Records of Mongoloid and Control Patients*

	Age groups							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Premature								
Mongoloid	1	7	3	12	14	6	1	44
Control	1	3	4	2	1	1	0	12
Instrumental								
Mongoloid	1	5	4	5	7	8	0	30
Control	2	5	5	3	2	5	0	22
Prolonged labor								
Mongoloid	1	2	1	3	6	6	1	20
Control	1	3	4	1	0	0	0	9
Cesarian								
Mongoloid	0	0	0	1	1	1	0	3
Control	0	2	1	2	1	0	0	6

TABLE 30 —*Miscarriages and Stillbirths in 255 Mothers Having a Mongoloid Child*

Age groups	No	No of mothers having miscarriages	No of miscarriages before and after Pt		Total	%
			Before	After		
15–19	4	1	1	0	1	25
20–24	26	5	0	5	5	19 2
25–29	29	7	6	6	12	24
30–34	48	19	21	7	28	39.3
35–39	84	29	42	12	54	29
40–44	56	15	19	1	20	26.9
45–49	8	4	6	0	6	50
Total	255	80	95	31	126	31.2

has attracted much interest on the part of obstetricians and pathologists. In a recent article A. T. Hertig and R. G. Livingstone reviewed this subject and found the incidence to be 10.6 per cent. The summarized findings of various authors indicate that 9.8 per cent of all pregnancies terminate in spontaneous abortion. In families in which a mongoloid child is born, the average for the whole group is 31.2 per cent, with variations from 19 2 per cent to 50 per cent, according to age groups This indicates a three times higher rate of spontaneous abortions than in the general population The material of the Lying-in Hospital, Boston, investigated with regard to mongolism by Beidleman, revealed an incidence of 19 per cent abortions, or twice the number of the control group.

The high incidence of abortions has recently led M Engler to find the "sole cause" of mongolism in a preceding artificial or spontaneous abortion which has caused "a serious alteration of the mucous membrane of the uterus." The implanted ovum finds pathologic conditions which hamper its nourishment This is a revival of the old nidation theory, with the modification that not chronic but acute changes in the uterine mucosa are the cause The incidence of previous abortions (in Engler's own material, 18 9 per cent), however, is far too low to base a theory of faulty nidation on it Moreover, the many normal children born after a mongoloid make the uterine nidation theory still less tenable. The frequency of abortions is an important clinical symptom, the interpretation of which will be given later.

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Probably closely related to the frequent miscarriages is another phenomenon. Many times the mother has observed a continuation of

Case Reports

As emphasized on different occasions, the factors which seem to lead to mongolism in the child are different according to the age of the mother. In the following, a number of case histories are presented to demonstrate the various conditions at different age levels

GROUP I: *Women Above Forty Years*

Case 1 Age 52 * Italian woman, big and stout Mongoloid is product of eleventh pregnancy The first 7 children are normal; some are married and have children of their own. Eighth pregnancy ended in a miscarriage, the ninth child died [illegible]

[illegible] sick all the time" She did not expect to become pregnant at that age

Case 2 Age 47 Had four children by her first marriage when she was between 23 and 35 She was a widow for five years and married again when 44 years of age. By this second marriage she had one child who is intelligent and in good physical health *Menopause* occurred at 46, and she had not menstruated for six months when new pregnancy occurred which ended in the birth of a mongoloid She did *not believe she could become pregnant*

Case 3 Age 46 Married in 1923 and did not become pregnant until 1930, when an *antiflection of the uterus* was straightened out and tubes dilated. She became pregnant after *that operation* There was an interval of eight years between the first and second pregnancy, in which time mother did not become pregnant in spite of *desire for a second child* Suddenly became pregnant at 46 and gave birth to a *mongoloid child* Put on 20 pounds during pregnancy, easily upset

Case 4 Age 46 Child is product of ninth pregnancy First 7 pregnancies normal During the eighth pregnancy mother developed high blood *pressure and had to stay in bed* for the last seven weeks After three years became pregnant again, and pregnancy *resulted* in a mongoloid child Condition during pregnancy was poor, high blood *pressure* Had to stay in bed for 4½ months Easily upset, anxious, easily fatigued

Case 5 Age 46 Ch[illegible]
now 32 m[illegible]
22 [illegible]
chi[illegible]
the [illegible]

[illegible]

[illegible] inches in height
45, d[illegible] Two miscarriages When
[illegible] last pregnancy resulted in birth of a
mongoloid baby Rather tall *woman*, 5 feet 10 inches Weight 165 pounds Had

* The age of the mother refers in each case to the age *when her* mongoloid child was born

born at the Lying-in Hospital. Twenty-five per cent of the mongoloid babies weighed 5 pounds 11 ounces or less. The incidence of prematurity in mongolism is, therefore, many times that of the hospital total. In my material, the incidence was 17.2 per cent.

Sterility

Of great interest are the difficulties that some mothers have in becoming pregnant. I observed many instances in which the mongoloid was the first or the second child and the mother had vainly waited many years for a pregnancy, or an unusually long time had elapsed between her first and her second child. Several times the waiting period lasted as long as 17 years. This decreased ability to become pregnant was evident in several instances before the mongoloid child was born. In many cases fertility was definitely impaired after a mongoloid birth. It is true that quite a number of children are born after a mongoloid and that the loss in fecundity is not absolute, but little attention has yet been paid to how severely the maternal fertility has suffered in cases of a mongoloid child being born in the mother's best years. Of the total of 255 mothers, 162, or 64 per cent, had no children afterwards Only one mother in three had a child after a mongoloid. This statement refers to the whole material. The picture is more striking if we consider only those cases in which the mongoloid appeared near the beginning of the childbearing period In 17 per cent of our material, the mongoloid was the first child, and in 45 per cent he remained the only child, in 73 per cent of the cases in which the mongoloid was a second child, he remained the last child. (In Lahdensuu's material 63 per cent of the first-born mongoloids remained only children, and 69 per cent of the second-born mongoloids had no younger siblings.) From the four mothers who had a mongoloid child between the age of 15 and 19 years, one had no other child and one had one child only afterwards Of the 26 mothers of the age between 20 and 24 years, eight, or 30 per cent, remained sterile for the rest of their lives Of the 29 mothers aged 25 to 29, a total of 16, or more than 50 per cent, remained sterile. These numbers prove beyond doubt that in the majority of cases the birth of a mongoloid child reveals a maternal condition which renders it unfit for childbearing afterwards. Since some investigators have tried to explain the drop in the birth rate by assuming that after the birth of a mongoloid child the mother is afraid to have more offspring, I have checked this statement carefully and found it irrelevant.

miscarriages, one before and one after her second (normal) child Did not become pregnant for eight years, no preventive measures taken. Slender woman, considered nervous Tall, weight 117. Prematurely aged. Lost weight and had metabolism test on account of suspected thyroid disorder

Case 21. Age 40 Married at age of 20 Had 2 children at 22 and 24, respectively Interval of 11 years between second and third child. No preventive measures, did not become pregnant

pregnant again

C

at 17

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mon

Both

blad ... very fatigued, white hair at 50

Case 24 ... years in spite of desire ... Two normal children a

Case 25 ... married at age of 25 Had 9 normal children ranging from 24 to 10 During tenth pregnancy, which terminated with birth of mongoloid baby, mother was threatened with abortion at four months Stayed in bed and hemorrhage stopped Had 2 more normal children at 42 and 44½

Case 26 Age 40 Married at 23 Both parents professional people Mother did not want children as long as professionally busy. After 15 years of married life, decided to have a child Pregnancy ended in birth of mongoloid

GROUP II *Women in their Thirties*

Case 27 Age 38 Married at that time, never before pregnant No pregnancy afterwards Stout woman with elephantiatic features, fair intelligence, kind Father temporarily alcoholic Mongoloid baby three weeks premature, weight 4 pounds 11 ounces

Case 28 Age 31 Married in her early twenties First pregnancy, miscarriage in second month Second pregnancy, three years after first, miscarriage at six months Third and fourth pregnancies

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goloid Parer

"safe times" ... conceived a few days after menstruation

nervous breakdown at the age of 27 when working hard in school and in stores Was ill about a year.

Case 8. Age 44. Three children by first husband, ranging from 19 to 15, and 6 children by second husband, all well Mongoloid child product of tenth pregnancy. Mother sick with renal hypertension and cardiac disease. Nervous, high-

icy during the last 18 years.

Case 10. Age 43. Married in 1919 Three normal children between 1926 and 1930 Mongoloid was born *after interval of seven years Menstruated twice during* pregnancy. At second month had a large hemorrhage and loss of blood It was thought to be a miscarriage.

Case 11. Age 43 Both parents in their forties. Married late, but urgently wanted a child Mother finally became pregnant, and a boy was born, to the great joy of the whole family. The doctors declared the child "perfect" Not until six months later was it realized that the child was abnormal, although the mother had *been suspicious and had consulted several doctors to hear their opinion*

Case 12. Age 42. Married at age of 19 First child at 20 One miscarriage after first child Was separated 10 years from husband, he being in Italy Had 1 normal children between 1930 and 1935 After seven years, pregnant again, resulting in mongoloid child. Did not expect child, was "careful." Child not wanted Mother sick all the time during pregnancy. Italian woman, stocky, gallbladder trouble, easily upset, fatigued

Case 13. Age 42 *Married at 29, had 6 normal children between 30 and 39.* Three year interval New pregnancy accepted, but not expected, ended in birth of mongoloid

Case 14. Age 42 Marriage at 23, 6 normal children between 21 and 39 There were six years between fifth and sixth child, when mother did not become pregnant in spite of opportunity and desire After three more years new pregnancy occurred which resulted in mongoloid baby Mother was diagnosed as thyroid *deficient with signs of puffiness and low metabolism, two years before her sixth* child, when she did not become pregnant Two grains of thyroid daily since then Her last child was first diagnosed as cretin, later diagnosis of "cretinism, mongolism" was made in outstanding hospital

Case 15. Age 41 Married at age of 36 Mongoloid is product of first pregnancy(!) after five years' waiting. There are 3(!) normal siblings who were born

) normal children between
id product of tenth preg-
nancy. Not expected; accepted, but not wanted Mother felt tired, depressed, did not feel life of baby There were two miscarriages between second and third and fifth and sixth pregnancies, respectively Two miscarriages after mongoloid

Case 17. Age 41. Mother married at 39 Had spontaneous (?) abortion at two months during first pregnancy, when almost 40 Second pregnancy terminated in *mongoloid* baby Enlargement of thyroid had been diagnosed two years before marriage, and treated Had 2 normal children after mongoloid at age of 42 and 43.

Case 18. Age 40 Italian woman, said to be very nervous and excitable First

nal child

Case 42 Age 31 Married at 22 Six years after marriage, first child Waiting time partly voluntary Wanted another child after first, but did not become pregnant for two years Mongoloid three weeks premature. Menstrual history: menarche at 15, a whole year only twice Later every second or third month, till shortly before pregnancy with first child Slender woman, 117 pounds

Case 43 Age 33 Married at 22 Did not become pregnant till ...

one ovary Ovarian cyst, uterus fibrosis Stout, obese woman, prematurely aged

Case 45 Age 38 Married at 23 in 1926 Had her first child in 1928, a healthy girl Not pregnant for 12 years in spite of desire to have another child Second child a mongoloid

Case 46 Age 36 Married at 28 in 1935 First child in 1938, normal boy Did not become ...

... mor betwe ... with radiu ... pregnancy ... strong wor ... had hysterical fits before every menstruation

Case 49 Age 38 Married at age of 30 First baby died at birth Large baby, birth injury Three months after birth mother was operated on for ... ovar ... sar ... pre ...

... married at age of 21 in 1927 Had 2 normal children in 1928 and 1929, respectively Became blind on account of kidney trouble, edema, eclampsia with convulsions Next 2 children, born in 1933 and 1936, were normal In 1939, mother operated for ovarian cyst Two years later, pregnant with twins One of twins normal, the other a mongoloid, blind Three years later, mother operated on for malignant tumor of ovary

Case 51 Age 39 Married at age of 23 Had 3 normal children in eight years following her marriage No pregnancy after third child for four years Fourth pregnancy ... nev ... rs after last living child, tra ... Child desired, no con-

... normal girl two years later Next pre... eight years later terminated in birth of mongoloid Child desired ... more than five years but no ...

Case 53 Age 35 ... in 1929 Miscarria ... the last pregnancy ...

Mother felt sick all the time, could not eat, felt difference between first and second pregnancy

Case 30. Age 38. Married at 35 One child at 36, small baby, one month premature. Two years later second pregnancy terminated with mongoloid baby. Next two pregnancies ended in miscarriages Thyroid of mother was noticed to be large. Very high-strung, excitable person, cries easily

Case 31 Age 30 First pregnancy ended in miscarriage in third month, second in second month. Mongoloid product of third pregnancy. Was threatened with abortion five months before delivery, but child was kept

Case 32. Age 38½. Married at 28 First pregnancy ended in miscarriage at three months One normal child at age of 37 One year later severe hemorrhages for several months Next pregnancy ended in premature birth of mongoloid Next year again severe hemorrhages No other child Thyroid reported enlarged Was twice operated on for "parathyroid cysts" Easily upset, worries considerably, gets "blue" spells

Case 33. Age 35 Mother married year before Mongoloid result of only pregnancy

Case 34. Age 37 Married at 20, menarche at age of 18 Cardiac disease Ovarian operation Six pregnancies 2 children alive and normal, 3 died, one at 18 months of rheumatic fever and two at 3 months of infections (?) Mongoloid child premature, pregnancy not wanted, gestation period poor

Case 35 Age 37 In first marriage 1 child, who died shortly after birth One miscarriage Married again at age of 34 Mongoloid is only child, born three years

ither high-strung, nervous

t 3 children normal Two years be-

e six years after last child Child

pregnant

Case 37 Age 30 Married at 19 First child at 20, normal and well No pregnancy for four years Second pregnancy ended with birth of dead baby, "had been dead about 1 month." After eight year interval, new pregnancy which ended with birth of mongoloid Child "very much desired" Mother 5 feet 1 inch tall, rather attractive, young looking Weight now 131 pounds Gained 75 pounds dur-

very.

gnancy

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After

Men-

struation irregular. Lasts seven days, terrible pains High-strung, easily upset, very nervous.

Case 39. Age 39. Married at age of 23 Had 3 normal children between 21 and

of mongoloid

int soon after marriage

child dead Did not be-

come pregnant for eight years in sp

maturely born. One year later new

strual bleedings, treated by x-ray

pregnancy terminated in birth of mongoloid Had continued to menstruate during two periods of the pregnancy

Case 41. Age 37. Married at 25 Had a normal child at 27 Ten year interval, which was only partly voluntary Child desired for quite a time Second pregnancy ended with birth of mongoloid

nancy ended in abortion by curettage Last pregnancy terminated with birth of mongoloid girl

Case 62 Age 42 Born in 1898, had goiter in 1926. Tremors, restless, nervous Married in 1929 Had two normal children in 1930 and 1932, respectively. Eleven months after second child, miscarriage due to shock from being beaten by insane person Next year, miscarriage due to "pills" Six years later, again took pills to interrupt pregnancy, but was not successful Felt very bad during whole pregnancy, inactive, could not sleep This pregnancy terminated one week prematurely

pected illegitimate child, not wanted, was mongoloid. Attempted abortion suspected

Case 66 Age 30 Married at

and 1932 A few months after

'pills" unsuccessfully Child n

goloid boy Next year again pregnant Took pills and bled for three or four weeks. Pregnancy ended in miscarriage in third month

Case 67. Age 28 Married at 20 in 1935 Had 4 normal children between 1936 and 1941 When again pregnant, two years later, took pills for several weeks. Child not wanted Pregnancy terminated about a week prematurely with birth of mongoloid boy

GROUP V. *Unexplained Cases*

In about 10 per cent of the material information

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biochemical studies of the mother

Summary

No one who glances through the series of case histories above can escape the impression that the condition of the mother at the beginning of pregnancy is of significance

Many investigators have studied the conditions under which mongolism occurs. Brousseau was able to obtain definite data concerning the health of the mother in 376 cases and found in 179, or 47 per cent, that the mother had been in ill health. Goddard goes so far as to state that "the sole and adequate cause of mongolian imbecility is to be sought in the condition of the mother during pregnancy." A rather

each menstrual term and stayed in bed After birth of mongoloid, irregular menstruation

Case 54. Age 35. First and only pregnancy of 35 year old woman ended in birth of mongoloid Child "accepted," mother's condition during pregnancy poor. Easily upset, unstable woman, asthma, now divorced

GROUP III: Women in their Twenties

Case [illegible]
severely [illegible]
lism —2[illegible]
with abortion. Stayed in bed for several days Mongoloid was born 10 days prematurely Mother allergic to chocolate, dust, weeds and certain foods.

Case 56 Age 28. Married at age of 23 First pregnancy started one month after marriage. Child died five months after birth, of bronchopneumonia Second pregnancy, six months after this child, ended in mis[illegible]
in miscarriage one year later Mongoloid is the [illegible]
uterine bleedings during this pregnancy. Had 1 [illegible]

Case 57 Age 20. Married at 18 and had her first child a year after marriage. Next year became pregnant again, child not wanted, but accepted Vomited every morning. Menstruation had been irregular since birth of first child At time of pregnancy, when third menstruation was due, had severe hemorrhages, lasting five days Stayed in bed for two weeks Pregnancy terminated in birth of mongoloid boy

Case 58 Age 23 Married in 1931 at age of 18, had her first child, a normal boy, in 1932. Another boy in 1933. Became pregnant again in 1936, used "safe days" in the interval Her menstruation was irregular and she had severe hemorrhages, lasting seven days, during which time she had to stay in bed During this pregnancy, [illegible]
enth m[illegible]
Mother [illegible]
overw[illegible]" and did not expect to become [illegible]

Ca[illegible] arche at 14, had irregular menst[illegible] 1940, normal child Very shortly after delivery, before normal menstruation was established, a new pregnancy started This pregnancy terminated six weeks prematurely in birth of mongoloid

Case 60 Age 21. Married at 20 Menarche at 11 Had menstrual trouble at 17, [illegible] physician in charge. Had infantile [illegible] pregnancy at time of second men[illegible] pounds during pregnancy, having weighed 125 pounds at the beginning. Mongoloid was born 25 days prematurely Had "flu" in the fifth month of gestation Her second child, born two years later, is normal

GROUP IV: Mongolism and Attempted Abortion

Case 61. Age 28. First child at 17, an imbecile of familial type. Second child, two years later, in 1929, said to be normal. After birth of this child, did not want another child Became pregnant five times between 1930 and 1937. Each preg

nancy ended in abortion by curettage Last pregnancy terminated with birth of mongoloid girl

Case 62 Age 42 Born in 1898, had goiter in 1926 Tremors, restless, nervous Married in 1929 Had two normal children in 1930 and 1932, respectively. Eleven months after second child, miscarriage due to shock from being beaten by insane person Next year, miscarriage due to "pills" Six years later, again took pills to interrupt pregnancy, but was not successful Felt very bad during whole pregnancy, inactive, could not sleep This pregnancy terminated one week prematurely in birth of mongoloid girl

Case 6

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Case 66 Age 30 Married at 19 in 1922

and 1932 A few month

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GROUP V. *Unexplained Cases*

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large number of investigators feel that thyroid deficiency is of importance. Clark, Stoeltzner, Myers, Alt, DeSanctis, Schob, Abderhalden and Vas express the opinion that either hyperthyroidism or hypothyroidism of the mother may account for the production of mongolism. Myers, in a study of 215 mongoloid cases and 215 controls, states, "Some abnormal condition in the mother during pregnancy was reported in more than twice as many of the mongolians as the control mothers An analysis of this difference in the health of the mother revealed a greater frequency of recognizable thyroid disorders (9 to 1) and of acute nervous excitement (13 to 1)."

Another explanation for the mongoloid deformity was offered by van der Scheer, in 1927. This author concluded that (1) "a too narrow amnion prevents or inhibits the physiologic stretching of the embryo in the sixth or seventh week of pregnancy, and (2) anomalies in the structure of the uterus are the cause of the abnormal amnion sac." This theory, called the "nidation theory," explains the great variety of deformities on the basis of mechanical factors. It is hardly necessary to repeat the numerous arguments which make it impossible to accept such a mechanical explanation Knowledge of the physiology of pregnancy has increased so greatly in the last decades that we know that delicate biochemical reactions take place in pregnancy, and hence, that the diversity of malformations seen in mongolism cannot be laid to so simple a common denominator as a narrow amnion sac. Moreover, some of the malformations date back to an earlier time than the sixth or seventh week, and those disorders take place at a time when mechanical pressure of the membranes is of no significance whatsoever.

In 1939 Horst Geyer analyzed very carefully the material of 33 cases. In rejecting other theories, he concluded that the essential cause was an inadequate "dysplasmatic" ovum Such ova occur in increased frequency at the time of menopause and occasionally in the menarche. Under pathologic conditions, especially cystic ovaries or illness of the mother, they can develop at any time of the life cycle Independently, Lotte Lande-Champain also came to the conclusion that ovarian dysfunction with ensuing fertilization of a "borderline" ovum must be considered the most likely explanation

The maternal factors analyzed in the 75 cases reported by Benda (1947) are tabulated in table 32.

Nine women (12 per cent of all cases, but 33 per cent of the women above 40) showed actual cessation of menstruation before the pregnancy which resulted in a mongoloid child The most impressive factor of all is the inability to become pregnant which manifested itself in involuntarily long intervals between pregnancies These intervals,

TABLE 32 —*Summary of All Causes*

	Number of instances	Incidence %
Actual cessation of menstruation (menopause)	9	12 1
Inability to become pregnant (involuntary long intervals)	22	29 2
Old primiparas	4	5 3
Habitual abortions	7	9 3
Numerous artificial abortions	2	2 6
Attempted abortions	7	9 3
Continuation of menstruation and threatened abortions	11	14 6
Thyroid deficiencies and goiter	10	13 3
Ovarian cysts and operations	6	8 0
X ray or radium treatment of uterus and ovaries	2	2 6
Gallbladder	3	4.0
Heart diseases	2	2 6
Depressive states	5	6 6
Kidney trouble	3	4 0
One of twins	1	1 3
New pregnancy immediately after another child	1	1 3
Unusual weight gain during pregnancy	1	1 3
No explanation	8	10 6

ranging from more than five to 18 years, occurred in spite of the desire of the parents to have a child. Twenty-nine per cent showed this inability The factor next in importance is the continuation of men[illegible]

[illegible] preventing uterine bleedings are at fault. Habitual abortions were found in 9 3 per cent of the material.

The prenatal maternal factors have been the subject of other investigations by the author during the last 10 years. The new observations confirm the previous material and provide still more evidence as to specific data.

Of the women above 41 years of age, 53.9 per cent were actually in

TABLE 33 —*Percentage Incidence of Significant Symptoms in Each Age Group*

Age groups of mothers (yr)	Menopause or menstrual irregularities before pregnancy (%)	Long interval (3-18 yr) before birth (%)	Bleedings during pregnancy (%)	Thyroid troubles (%)	Uterine and ovarian anomalies (%)	Placenta praevia (%)	Incidence of previous abortions (%)	Twin pregnancy (%)
41 to 52	53 9	92	0 8	0 8	15 4	0	36 2	0 8
31 to 40	47 6	81	48 8	38 5	63 5	14 3	19 0	0 8
21 to 30	23 1	46	38 5	38 5	23 0	0	38 5	0 8
15 to 20	67 0	33	67 0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

large number of investigators feel that thyroid deficiency is of importance. Clark, Stoeltzner, Myers, Alt, DeSanctis, Schob, Abderhalden and Vas express the opinion that either hyperthyroidism or hypothyroidism of the mother may account for the production of mongolism. Myers, in a study of 215 mongoloid cases and 215 controls, states, "Some abnormal condition in the mother during pregnancy was reported in more than twice as many of the mongolians as the control mothers. *An analysis of this difference in the health of the mother revealed* a greater frequency of recognizable thyroid disorders (9 to 1) and of acute nervous excitement (13 to 1)."

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The maternal factors analyzed in the 75 cases reported by Benda (1947) are tabulated in table 32

Nine women (12 per cent of all cases, but 33 per cent of the women above 40) showed actual cessation of menstruation before the pregnancy which resulted in a mongoloid child. The most impressive factor of all is the inability to become pregnant which manifested itself in involuntarily long intervals between pregnancies. These intervals,

TABLE 34.—*Distribution of Factors Held Responsible for Ovarian Dysfunction in 150 Cases of Mongolism*

Leading etiologic factor	No. of cases
Group I—"Physiologic" exhaustion of an originally efficient reproductive system through overwork up to menopause	22
Group II—Primary ovarian dysfunction	60
Transitory primary ovarian dysfunction in adolescents	13*
Group III—Secondary ovarian dysfunction	68†
(a) thyroid deficiency	24
(b) acute or subchronic diseases	16
(c) rapid succession of pregnancies	6
(d) local disorders of ovaries or tubes	15
(e) psychic disturbance at time of conception	24
Unexplained	7

* These 13 cases [illegible]

† Since seve[illegible]
women appear [illegible]
groups is more than 68. Also, in 7 mothers, primary and secondary ovarian dysfunction seemed of equal importance, therefore these cases appear in group II as well as in group III.

From Lande Champain, L. The etiology of mongolism. J. Child Psychol. *3*: 53, 1954.

Evidence for ovarian dysfunction was summarized by Lande-Champain (1954) in observations on 150 cases (table 34).

THE NUCLEAR PATHOLOGY OF THE ZYGOTE

In the chapters on pathology and biochemistry, I have provided evidence that mongolism is associated with cellular pathology which involves [illegible] doctr[illegible] tion [illegible] mongolism but rather a generalized inadequacy of metabolism of the cells which compose the organism. Thus [illegible] appears [illegible]

[illegible] function

While chromosomal anomalies in abnormal sex differentiation have been well established, a new discovery in the field of genetocytology came in 1959 when Lejeune, Gautier and Turpin studied human chromosomes in tissue cultures and reported a supernumerary chromosome in mongolism. These findings were confirmed almost immediately by Ford et al. In the meantime, further evidence has been collected at different institutions.

the menopause or showed evidence of approaching the menopause by irregularities of menstruation; 92 per cent had an interval of 3 to 16 years before the pregnancy that resulted in the birth of a mongoloid child. In the maternal age group of 31 to 40, 48.8 per cent had bleedings during pregnancy, 38.5 per cent had thyroid trouble and 63.5 per cent had a history of uterine and ovarian dysfunction. In the maternal age group of 21 to 30, a long interval was found in 46 per cent, and 38.5 per cent had bleeding during pregnancy and thyroid disorders. In this group, the incidence of previous abortions was also 38.5 per cent. In a group of women 18 to 20 years of age, more than one-half of them had menstrual irregularities before they became pregnant and also had bleedings during pregnancy. Most outstanding in this new study is the high incidence of thyroid disorders (38.5 per cent) in the younger age groups. The advanced age group did not reveal such a high percentage. A relationship between thyroid disorders and mongolism has been found by Myers in a study of the geographic distribution of mongolism in the province of Ontario, Canada

The material indicates that potentially, under certain conditions, every mother can give birth to a mongoloid child If the families recorded above had not had a mongoloid among their children, the group as a whole would certainly represent a sample above average in intelligence, health and fertility

A temporarily faulty oogenesis develops in previously healthy women who—in a large percentage of cases—have given birth to normal children before and are able to give birth to normal children afterwards.

Mongolism manifests itself as a disorder of cellular activity, possibly due to some abnormal events at the time of fertilization The observations add evidence to the statement that mongolism is not a hereditary disorder, nor can mongolism be considered a "spontaneous mutation" because it must be looked upon as an induced mutation due to abnormal conditions in the maternal organism Fertilization of an abnormal ovum has been postulated by numerous investigators, and evidence of ovarian dysfunction has been seen in many cases. In women beyond 40, the idea that the fertilized ovum may have been "overaged" is not surprising Observations that the interval between pregnancies is relatively long in most instances of mongolism further suggests that an ovum may occasionally be fertilized after resting in the ovary beyond its due time. Moreover, the "hormonal sterility" which I demonstrated suggests that maturation and regular release of ova may be at fault.

TABLE 34—*Distribution of Factors Held Responsible for Ovarian Dysfunction in 150 Cases of Mongolism*

Leading etiologic factor	No of cases
Group I—"Physiologic" exhaustion of an originally efficient reproductive system through overwork up to menopause	22
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(c) rapid succession of pregnancies	6
(d) local disorders of ovaries or tubes	15
(e) psychic disturbance at time of conception	24
Unexplained	7

* These 13 cases are included in the 60 cases of group II.
† Since several factors, as specified in the subgroups, were present in some cases, these women appear in more than one subgroup This will explain that the sum total of the 5 subgroups is more than 68 Also, in 7 mothers, primary and secondary ovarian dysfunction seemed of equal importance, therefore these cases appear in group II as well as in group III
From Lande Champain, L The etiology of mongolism J Child Psychol 3 53, 1954

Evidence for ovarian dysfunction was summarized by Lande-Champain (1954) in observations on 150 cases (table 34).

THE NUCLEAR PATHOLOGY OF THE ZYGOTE

In the chapters on pathology and biochemistry, I have provided evidence that mongolism is associated with cellular pathology which involves every organ system It is therefore not a specific organ or endocrine system which can be held responsible for the inadequate function found in mongolism but rather a generalized inadequacy of metabolism of the cells which compose the organism. Thus mongolism appears to be a molecular disorder in which the growth deficiency depends on a disorder of cellular growth regulation. The cause of this generalized growth deficiency must be sought in some disorder of the organizers and enzymatic function.

While chromosomal anomalies in abnormal sex differentiation have been well established, a new discovery in the field of genetocytology came in 1959 when Lejeune, Gautier and Turpin studied human chromosomes in tissue cultures and reported a supernumerary chromosome in mongolism. These findings were confirmed almost immediately by Ford et al. In the meantime, further evidence has been collected at different institutions

For a better understanding of these events, we may briefly consider the process involved in cell cleavage. As mentioned, the separate "chromosomes" are actually parts of a very intricate chromatin coil which represents the structure of the cell nucleus. Under resting conditions, the chromosomal rods cannot be recognized, and it is only when a cell is in cleavage that the very complicated process of chromosomal formation and disjunction occurs. Each species has a standard number of chromosomes; and man is now considered to have 23 chromosomal pairs, which gives him a total of 46. In the fertilization of the ovum, the 46 chromosomes of the new zygote are composed of 23 derived from the father and 23 derived from the mother. In this way the new being has the same number of chromosomes as the parental organisms. Before fertilization, ovum and sperm undergo cell divisions and throw off half of their chromosomes in order to arrive at the number of 46 when both nuclei join. The possibility has to be taken into consideration that under certain conditions an overaged ovum has thrown off not 23 but 22 chromosomes, for example, and therefore contains a supernumerary chromosome at the time of fertilization by the sperm Such abnormal cells have been observed in animals, and since there is much evidence that ovarian function in the mothers of mongoloids is often at fault, the possibility exists that an ovum with a supernumerary chromosome had been fertilized.

As is obvious from this report, the cell cleavage is not a matter of "genetics" but of the life of the total cell. The differentiation of the chromatin coil into chromosomal rods, and the development of the centrosomes and the even cleavage of the cell, depend on the total life of the cell and its vitality, and not on the chromatin particles themselves.

If the supernumerary chromosome found in mongolism is a manifestation of inadequate disjunction and, therefore, abnormal distribution of chromatin in some cells, the impairment of the cytoplasm probably took place in the preparatory cell divisions of the maturing ovum, which was then fertilized, or in the earliest stages of the fertilized zygote cleavage It is rarely recognized how complicated the metabolic processes of the enzymatic systems are and that, at different periods of development, different and new functions are constantly required by the same gene systems according to the stage of development that has been reached. Keeler points out that:

Very little is known about these processes accompanying the first 44 generations of embryonic cell division .. we may name a few that have been recognized .

[illegible]

mic substances thus created may react with the chromosomes or be transferred to other cells where they react on the cytoplasm to produce other substances. (5) The presence of a twin may produce changes by inter embryonic induction such as seen in the reversed characters of twins (6) A series of growth rate potentials, polarity mechanisms and organizator forces is indicated (7) We have noted the highly important reciprocal reactions between placenta and foetus (8) During pregnancy, the corpus luteum is stimulated by the anterior pituitary hormone, Prolan B (9) The influence of the ovary produced Progestin upon the uterus [is noted] (10) [There is an] effect of the Corpus luteum upon the foetus *

Figure 82 demonstrates the chromosomal assortment in a male with mongolism, arranged according to the classification used at present by Chu and Giles As yet, there is no uniformity in classifying the chromosomal assortments. Lejeune uses a numbering system that is slightly different from the one used by Ford et al. In America, it has become standard procedure to count the autosomes according to size and distribution of centromeres, from #1 to #22, and to count the sex chromosome pair separately as #23 I have followed this standardization, and an idiogram† of the normal human chromosomes as drawn by Chu and Giles is included in figure 82. As will be seen, this patient has three instead of two autosomes #22.‡ There is a Y chromosome of similar size and an X chromosome, indicating that the sex chromosomes seem normal, in spite of the fact that there were clinical suggestions of the Klinefelter syndrome combined with mongolism, as have been described by Ford et al

Figure 83 shows a chromosomal assortment similar to that in figure 82 in a female patient having two X chromosomes and 22 autosomes with one supernumerary fragment associated with autosomal pair #22

The interpretation of these new observations is still a matter of controversy The first reports noted the finding of a "supernumerary" chromosome Geneticists, however, distinguished two forms of abnormal chromosome assortments "Supernumerary" or accessory chromosomes are chromatin fragments, the significance of which is not definitely established. They may be heterochromatic chromatin

* Quotation from "The value of animal experiments to the understanding of human genetics" *Medical Genetics and Eugenics* Philadelphia, Women's Medical College of Pennsylvania, 1940, pp 98–100

† Courtesy of Dr Chu

‡ Ferguson Smith counted 65 plates "Forty-nine have clearly got 47 chromosomes" (Personal communication)

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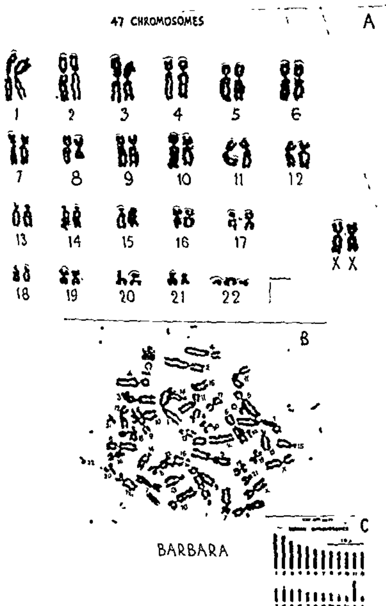


Fig. 83.—Chromosomal assortment of a female patient (Barbara) with mongolism (A) (B) (C). For description, see figure 82. Note under #23 a supernumerary chromosome of a trisomic configuration

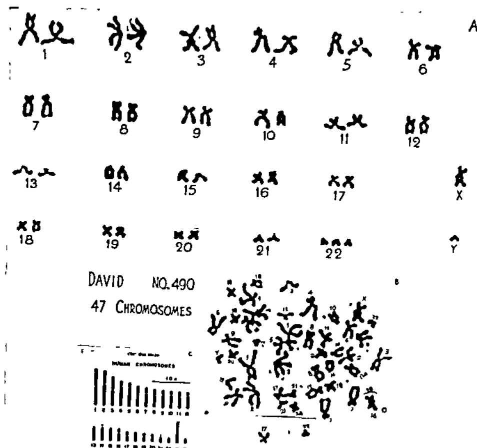


FIG 82.—Chromosomal assortment of a male patient (David) with mongolism. (*A*) The chromosomes of a cell, taken from a photograph and arranged according to chromosomal numbering of Chu and Giles *Note* under #22, 3 instead of 2 chromosomes of equal size (*B*) Photomicrograph of the actual chromosomal as-

material with no specific genetic or enzymatic function. Observations on supernumerary chromosomes in many different animals species suggest that these chromatin fragments are made up of nonspecific genic material. The question of whether the accessory chromosome in mongolism is genetically active cannot yet be decided. According to size, it is an autosome and may carry genic material of the same nature as autosomes #22 or #21. On the other hand, it cannot be denied on the basis of histologic studies that the supernumerary chromo-

some is also the same size as the Y chromosome; and since sex anomalies are extremely frequent in this condition, a relationship to the Y chromosome cannot be excluded

It is now thought by many investigators that the third autosome is not a "supernumerary" chromosome, but that the autosome complement 22 is trisomic. This would mean that in addition to the normal chromosome complement, there is either 1 (simple trisomic) or even 2 (double trisomic) chromosomes attached to one pair. This would indicate that the original cleavage of chromosomes in meiosis has misfired and a nondisjunction has taken place, leaving the fertilized zygote a 24 chromosome assortment fertilized by a 23 chromosome sperm, with the result that the offspring carries an assortment of 47 chromosomes in his somatic cells. The situation is demonstrated in figure 81, which shows the different stages of meiosis and mitosis of a cell with a normal assortment of 8 chromosomes (instead of 23 chromosomes) Under #8 of this figure, the occurrence of an abnormal chromosome distribution can be seen insofar as the cell on the right has one extra chromosome (S Chr.) whereas the cell on the left has one chromosome too few.

The interpretation of these findings rests on several questions:

1. If the accessory chromosome in mongolism represents a trisomic incidence, it is likely that it is the result of a nondisjunction at meiosis before the ovum was fertilized Mongolism in this case is the result of fertilization of an abnormal, possibly "overaged" ovum, for which there is considerable clinical evidence This theory is well supported by the facts of advanced maternal age or—in younger women—fertilization after an unusually long interval between two pregnancies

2 If not all somatic cells have a trisomic assortment of pair 22 and some are found to have 46 or 48 or other chromosomal assortments—for which there is some evidence in my bone marrow studies—we deal

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in each of the two cells in formation (7) Two cells with new sets of 8 chromosomes before cleavage is completed (8) A theoretical assumption that in cleavage, one centrosome has attracted 9 chromosomes while the left half of the cell has but 7 chromosomes. The 7 chromosome cell may die (a lethal mutation) while the 9 chromosome cell may become fertilized or is already a fertilized cell and will be the origin of an organism with a supernumerary chromosome (S Chr) (9) Drawing after a mitotic metaphase of a bone marrow cell in mongolism (according to Ford and co-workers Lancet, April 4, 1959, pp 709–710) counting in-dicates the presence of ? X... considered by th... and the Klinefel... arranged accor... corresponds to ... is not counted as #7 but as #23 The abnormal supernumerary chromosome seen in (9) is to be classified as #22

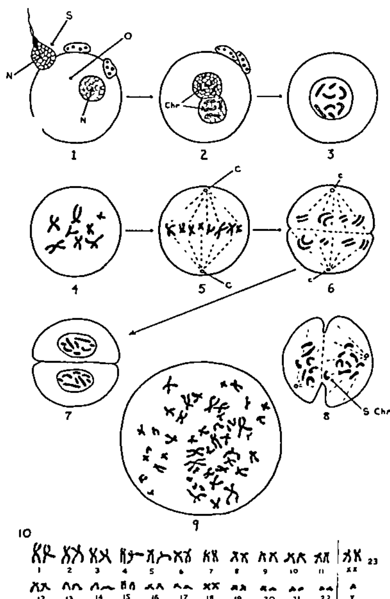


FIG. 84—Diagrammatic representation of fertilization of an ovum, and one of the possible ways of abnormal chromosome distribution It is assumed that the species under observation has 8 chromosomes (instead of the 46 in man) (*1*) Fertilization of an ovum (O) by a sperm (S) Both cell nuclei (N) have chromatin coils in which the chromosomes are not clearly differentiated. Before synapsis (junction of sperm nucleus and nucleus of ovum), each cell throws off half of the normal chromosomes by maturation meiosis (*2*) The two nuclei, each with 4 chromosomes (Chr), unite (*3*) The newly fertilized ovum contains 8 chromosomes, 4 paternal and 4 maternal (*4*) In synapsis, the homologous chromosomes form pairs (*5*) Two centrosomes (C) are formed, which orient the chromosome pairs into a plane from which 4 pairs move to each side into the newly formed cells (*6*) Mitotic metaphase, in which 4 chromosome pairs (8 chromosomes) are moving

some is also the same size as the Y chromosome; and since sex anomalies are extremely frequent in this condition, a relationship to the Y chromosome cannot be excluded.

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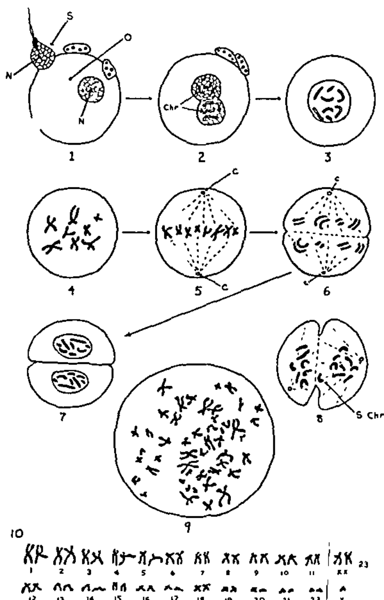


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lished anomalies in the karyotype as a result of many different noxious agents, e.g., radiation (Puck, Griffen and others) and chemicals (Benzer and Freese and others), to mention two types. Under abnormal environmental conditions the karyotype shows translocation, ring formations, dicentric figures and fragmentation. Under experimental conditions it is possible to compare the results with sufficient normal controls, but this is not yet possible in human pathology. Human

open up a new field for extensive research along the lines already opened up in cancer research and investigations into the influence of certain chemical agents on nuclear activity. It may be anticipated that genetocytology will have reached a point in the next decade at which anomalies of the karyotype can be considered a true expression of either an abnormal inheritance or mutations in the genetic endowment.

We may summarize that an understanding of the etiology of mongolism has become possible in recent years. Mongolism is a deceleration of growth and differentiation

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tion in which the life of the cell is impaired through the presence of abnormal chromatin material which is apt to exercise an abnormal or inhibitory influence upon the cell. In this way the cellular life of all organ systems is impaired. The cause of this disorder must be sought either in the fertilization of an abnormal ovum or the impairment of the cytoplasmic structure in the early stages of cell cleavage with resultant misfiring of the chromosomal disjunction. The ovum is then trisomic for one of the small acrocentric autosomes (#22 or #21, according to the newer counting) "due to the failure of both members of a pair of

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* Jacobs et al.: The somatic chromosomes in mongolism. Lancet, 1959, p. 710.

with a mosaic in which certain somatic cells reveal abnormal cell mitosis while other cells either maintain a normal assortment or show even more striking anomalies in chromosomal distribution. It remains to be seen whether the different chromosomal counts in cells are the result of artifacts, and of no clinical significance, or are a true expression of abnormal cell metabolism. In the latter case, the mosaic distribution of abnormal chromosome numbers may indicate a general molecular pathology which would not necessarily be due to fertilization of an abnormal ovum but could be due to noxious factors operating during early stages of gestation. Under these conditions, the question of whether mongolism is due to fertilization of an abnormal ovum or occurs in the early stages of pregnancy is not yet decided.

3. If the supernumerary chromosome is a true additional chromosome, there is still the question of whether we deal with a fragment of genetic significance or unspecific chromatin matter. A gene represents an enzymatic system which controls a metabolic sequence. The presence of an additional enzyme system could easily interfere with normal cell metabolism and could throw "a monkey wrench" into the smooth operation of cellular metabolism. Such additional enzyme material can have inhibitory action in certain stages of development as well as stimulate other processes at the wrong time. The abnormal deceleration of growth and the faulty synchronism seen under such conditions support such a theory.

4 An analysis of the whole karyotype of a cell (the chromosomal constitution) reveals that there is a great variety of single chromosomes in each assortment. The chromosomes have been arranged according to present standards in figures 82 and 83. It is obvious, however, that many of the larger chromosomes show variations in size and shape, some seeming to lack portions of their chromatin structure The supernumerary chromosome could easily be attached to one of the incomplete individual chromosomes, thus constituting a well-shaped pair It is therefore possible that we are dealing merely with an increased fragmentation and translocation of chromosomes, an observation frequently made in animal experiments Hence, great caution should be exercised in the final evaluation of abnormal findings

5. As Curt Stern points out· The number of chromosomes alone is only one informative aspect of the chromosome assortment Analysis of the karyotype includes not only numbers but size, shape, and other individual characteristics of the chromosome.

Such qualitative analysis in the human genetocytology is an area of research which is still at its very beginning In different species, genetocytology has estab

Such pathology interferes with the process of cell cleavage, with possible chromosomal nondisjunction or translocations and appearance of chromosomal breaks and mosaic formations. Under such conditions, an increased number of cells may have abnormal numbers of chromosomes or "sticky" nonseparation or breakage. Such chromosomal anomalies interfere with the distribution of enzymes and produce a dysfunction of balance and synchronism. This is exactly what we observe in the mongoloid child.

Observations on the incidence of mongolism indicate that the appearance of a mongoloid child in a family usually occurs after the birth of perfectly normal siblings. Thus the condition underlying mongolism cannot be some persistent anomaly in the maternal organism or caused by maternal gene mutation. If the mongoloid child is born as the first child or in the middle of a line of siblings, we see that perfectly normal children are born after the mongoloid. We are therefore dealing with a temporary condition in the mother. Yet certain observations indicate that the mother's fertility seems to be lessened after the birth of a mongoloid and that lethal mutations may increase, as indicated by the frequency of abortions before and after the mongoloid birth.

Studies of the maternal organism have indeed failed to produce any evidence of persistent anomalies in the maternal organism. This will not surprise one who considers the observations reported above. However, the findings with respect to chromosomal aberrations make it desirable to study the nuclear chromatin of mothers who have given birth to a mongoloid child or who seem to have fertility difficulties It is possible that increased numbers of mosaics may be found, with cells with varying numbers of chromosomes. Were these findings to be confirmed, one could assume that a critical period is present in which fertilization is not desirable.

After the birth of a mongoloid child, the question often arises whether or not the mother should and could have another child. The safest procedure is to weigh all factors which seem to have contributed to the appearance of a mongoloid child The mother should undergo a thorough examination, including a study of the endocrine system, in order to establish that conditions are favorable for procreation As long as chronic infections, nutritional and endocrine deficiencies and functional disorders are present, a new pregnancy does not seem indicated. It is not yet possible to make a detailed determination of the mutogenic factors and thus the necessary examinations; but with increased interest and experience, the constellation under which mongolism occurs will evolve

CHAPTER X

PREVENTION AND EMPIRICAL RISK

The likelihood that the mongoloid growth disorder is associated with chromosomal aberrations, thus being a nuclear molecular disorder, poses new problems for further research and possible prevention. Regardless of whether the chromatin anomalies are another symptom of the general disorder or represent the actual cause of the deficiency, the facts indicate that we deal with a chromosomal mutation which *must have occurred at the time of oogenesis or in the earliest stages* of embryonic development.

As pointed out in chapter IX, we are not dealing with a spontaneous mutation but with an induced mutation which apparently occurs on the basis of abnormal conditions in the maternal organism. As early as 1946, I pointed out that the mongoloid child occurs under threshold conditions of hormonal sterility The newer observations of the last fifteen years fit well into the framework of observations collected through animal experiments: that if the maternal organism is exposed to pathologic conditions which interfere with oogenesis or chromosome divisions, rates of mutation in the offspring increase greatly and the likelihood of producing an abnormal offspring is multiplied.

Regardless of the type of noxious factor—whether x-irradiation or chemical, hormonal, nutritional or focal—a period of sterility is usually preceded and followed by increased anomalies in the offspring. Evidence has been collected that mongolism is due to maternal factors, at least in the majority of cases, since certain characteristics of the mongoloid child indicate a closer relationship of its cellular reactions to the maternal than to the paternal organism We have provided evidence that one of the most characteristic features in the histories of mongoloid offspring is the fact that there was a period of inability to conceive As may be seen from tables 35 and 36, the "long interval" before the birth of a mongoloid child is one of the most persistent observations In addition to this, many more details indicate that the maternal organism had been exposed to adverse factors which might interfere with oogenesis, at least temporarily.

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Under present conditions, what are the empirical risk figures for having another mongoloid child?

EMPIRICAL RISK FIGURES

For all families that have experienced the birth of a mongoloid child, the question of whether they should or should not have more children is a matter of grave concern: Can they have more children without risk of having a second mongoloid child? And even people who are not directly concerned ponder the question of "hereditary" implications and seek professional information In view of the large number of mongoloid births, the physician's advice is a matter of great responsibility.

In an article on "Empiric risk figures in mongolism," J. A. Böök and S C. Reed in 1950 stated, "What physicians actually want to know for counseling is not the frequency of mongolism among all siblings but the risk figure for children born after the appearance of the first mongoloid child in the family." Böök and Reed found that the woman who has borne a mongoloid child has one chance in 25 to bear a second, or an actual risk 20 to 60 times greater than if no mongoloid child had been born. They based their calculations on an evaluation of the literature and not on original research, relying heavily on an earlier study by Penrose which had been completed previous to 1939. Böök and Reed quoted Penrose as having found such a high risk figure, namely 3.9 per cent. They claimed that 6 of 153 siblings born alive subsequent to the first mongoloid child were mongoloids.

Every clinician with extensive experience in mongolism can testify to the rarity of its familial occurrence, in contrast to other genetic conditions such as phenylpyruvic amentia, gargoylism, amaurotic idiocy, cleft formations, and others Only in very few cases is a second *mongoloid child born into a family In a study of 255 mongoloid* children and their families, I found only one case of a second living [illegible] subsequent to [illegible] per cent [illegible] clinico-genea- [illegible] on Seeland and neighbor- [illegible] n reports on the familial [illegible] that the high incidence [illegible] inhart (Switzerland, 1941) is not in accord with any of the other published reports. Of 354 mongoloids born alive, Øster found six instances in which there was a younger *mongoloid child.*

It is apparent from the foregoing that the findings of different investigators vary. It is possible that some of the reports of studies made ten to twenty years ago of "familial" cases of mongolism contain a number of mistaken diagnoses. Of 15 cases of gargoylism seen by me personally in the last few years, five came with the diagnosis of mongolism from other physicians or clinics. Knowing the great familial incidence of gargoylism, one may wonder whether the statistical study of Penrose's relatively small material (which was collected between 1934 and 1939, at a time when gargoylism was practically unknown and difficult to evaluate) included some other conditions. This seems even more true of Hanhart's reports, in which the mongoloids of Swiss institutions were evaluated—institutions in which a great variety of conditions (cretinism, gargoylism, hypertelorism, and other anomalies) are massed together. A few erroneous diagnoses could well upset the whole statistical value of such investigations.

The empirical risk of having a second mongoloid child must be considered no greater than the risk in advanced maternal age. Other investigators are in accord with this statement, i e., Engler (1949), who considers the occurrence of a second mongoloid as pure accident.

Mongolism on a "familial" basis is apparently a problem in itself. Here we must assume that there are specific (possibly genetic) factors which are not present under average conditions I can cite three cases: a family in which all three children were mongoloids, another with two of four and another with two of three children. In only one instance have I seen two mongoloids among 13 siblings, 11 of whom were perfectly normal children Similar observations have been made by other investigators In a case presented by D Jolly,* twin sisters each gave birth to a mongoloid child

Several investigators who have dealt with mongoloid twins are of the opinion that the birth of a mongoloid child indicates changes in the maternal organism which are not always reversible. Allen and Baroff, for instance, state that the etiology does not rest on a temporary, passing influence during pregnancy but on more or less persistent changes in the procreative or endocrine system of the mother.

PREVENTION

These considerations have a bearing on the question of whether mongolism can be prevented or its frequency at least reduced It is obvious that the clear relationship to advanced age indicates that

* Case discussed by Dr Jolly at the First International Medical Conference on Mental Retardation, Portland, M...

the incidence of mongolism would be reduced if pregnancies are discouraged after the age of 40 and true caution is exercised in the menopause. That there is very much need of sound advice is pointed out by the many accounts of mothers who had thought that irregular menstruation or even cessation placed them beyond the risk of having a child, and who then gave birth to a mongoloid child.

Women in Their Forties

What are the outstanding factors in mothers of mongoloids in this age group? A considerable number of them have had many children (five to 12), which is more than one would expect in a society in which two to three children are the average. There is the oft-repeated story of many children, then one or two miscarriages, and finally the period of menopause when the mother thinks that her family is "complete" Contrary to expectations, she suddenly becomes pregnant; and the pregnancy continues despite poor health and some bleedings. Poor health may consist of high blood pressure, kidney or heart trouble, or unspecific complaints of being tired and worn out. Obviously this woman must be kept under careful observation and subjected to further studies.

Then there is the woman in her forties who has had no children or who had a few children many years ago (five to 18 year interval) and who suddenly finds herself confronted with a pregnancy It may be a case of marrying late in life, or of a second marriage and wanting to give the second husband a child of his own Though most mongoloids are "wanted" children, some occur against all expectations as in the cases of "women with long intervals" I have made these intervals the subject of a special inquiry and have found that the intervals were involuntary in most instances; in spite of their desire, they had not become pregnant. Some investigators believe that a sudden rise in susceptibility occurs in the preclimacteric period, owing to increased estrogen production before the cessation of the cycle. Some women in my material had waited in vain all their lives, only to have impregnation take place in that critical period

Factors other than advanced age are presented in table 35 As will be seen, the first three cases were actually in the menopause, and pregnancy took place against expectation Menstruation was still regular in some of the subjects around 45 years of age, but the women had had no children for a long time We find both categories: (1) the woman with many children, the mongoloid being the last in a long line, and (2) the woman with no other children, or with few children and those born many years earlier.

. . . . . Present During

TABLE 35 — II

No	No of pregnancies before	Previous abortions	Threatened abortions	Menopause	Long interval	Deficient thyroid	Health during pregnancy
1	7	+		+			Poor
2	5			+			
3	0			+	+		
4	8				+		High blood pressure
5	12	+					
6	5				+		
7	6	+		+			
8	9						Renal hypertension
9	1				+		
10	3		+		+		
11	0				+		
12	5	+			+		Poor
13	6				+		
14	6				+	+	
15	0				+		
16	9	+					Poor
17	0	+	+			+	
18	5						Poor
19	3		?		+		Gallbladder trouble
20	2	+			+	+	
21	3				+		
22	8	+		+			
23			+	?			Liver, gallbladder trouble
24	2	+			+		
25	9		+				
26	0				+		Poor

By close observation of these few items, the physician will know when a case should include a careful endocrine examination as well as dietary and gynecologic management in the prenatal care

In summary, the most outstanding factors to be found in women of advanced age are habitual abortions, threatened abortion, menopause and previous inability to become pregnant in a period of more than three years This long interval need not be directly before the last pregnancy but may have been present during the prime of life

Women in Their Thirties

Here we are presented with a different picture The most outstanding factor is the inability to become pregnant Of 27 mothers, 17 (63 per cent) gave this history (table 36) If we observe that many

the incidence of mongolism would be reduced if pregnancies are discouraged after the age of 40 and true caution is exercised in the menopause. That there is very much need of sound advice is pointed out by the many accounts of mothers who had thought that irregular menstruation or even cessation placed them beyond the risk of having a child, and who then gave birth to a mongoloid child.

Women in Their Forties

What are the outstanding factors in mothers of mongoloids in this age group? A considerable number of them have had many children *(five to 12), which is more than one would expect in a society in* which two to three children are the average. There is the oft-repeated story of many children, then one or two miscarriages, and finally the period of menopause when the mother thinks that her family is "complete." Contrary to expectations, she suddenly becomes pregnant; and the pregnancy continues despite poor health and some bleedings. Poor health may consist of high blood pressure, kidney or heart trouble, or unspecific complaints of being tired and worn out. Obviously this woman must be kept under careful observation and subjected to further studies.

Then there is the woman in her forties who has had no children or who had a few children many years ago (five to 18 year interval) and who suddenly finds herself confronted with a pregnancy. It may be a case of marrying late in life, or of a second marriage and wanting to give the second husband a child of his own. Though most mongoloids are "wanted" children, some occur against all expectations as in the cases of "women with long intervals." I have made these intervals the subject of a special inquiry and have found that the intervals were involuntary in most instances; in spite of their desire, they had not become pregnant. Some investigators believe that a sudden rise in susceptibility occurs in the preclimacteric period, owing to increased estrogen production before the cessation of the cycle Some women in my material had waited in vain all their lives, only to have impregnation take place in that critical period.

Factors other than advanced age are presented in table 35 As will be seen, the first three cases were actually in the menopause, and pregnancy took place against expectation. Menstruation was still regular in some of the subjects around 45 years of age, but the women had had no children for a long time. We find both categories: (1) the woman with many children, the mongoloid being the last in a long line, and (2) the woman with no other children, or with few children and those born many years earlier.

Women in Their Twenties

Unfortunately there is not yet enough material for a statistical evaluation of women in their 'teens and twenties who have given birth to a mongoloid child. However, the individual observations of several investigators indicate that an "immature" maternal organism is as prone to produce a mongoloid child as an aging one. In a considerable number of cases, menstruation has not been regularly established before pregnancy.

In six cases of women in their twenties who gave birth to a mongoloid child, reported by me in 1949, one item was most striking: the frequency of threatened abortion. It can hardly be mere coincidence that five of the six pregnancies were threatened with termination by spontaneous abortion It may also be noted that in this group, and only in this group, three women gave a history of menstrual difficulties before the pregnancy. Most of the mongoloids born in this group were first children. It is suspected that the "threshold of sterility" is due to physiologic immaturity of the mother, whose organism is not yet ready for pregnancy.

Several additional instances of mongolism in first children of young mothers have been observed since the time of the original study. In these cases, menarche was sometimes delayed but usually normal. There was always a period of irregular menstruation prior to the birth

OTHER FACTORS

A number of interesting observations throw light on other essential factors which must be considered Statistics from countries which were exposed to extremes of disaster and malnutrition during the last world war indicate an increase in the incidence of mongolism (Klebanow, 1949) Most interesting is Hanbold's [illegible] ed on [illegible] birth [illegible] r than [illegible] statistics At the same time, the mongoloid's position in the birth order moved forward to an earlier place. Of 143 mongoloid children studied in Bavaria in the period after 1950, 74 per cent were born in the 10 critical years of war and malnutrition (between 1939 and 1949) while only 26 per cent were born before or after that period. Statistics giving the [illegible] total [illegible] that [illegible] unt [illegible] and [illegible] to reach a new high between 1947

TABLE 36—*Women in Their Thirties: Constellation of Factors Present During Pregnancy which Terminated in Birth of Mongoloid Child*

No	First pregnancy	Habitual abortions and miscarriages	Long interval	Thyroid disorder	Threatened abortion	Gestation period	Ovarian cyst
27	+						
28		+	+			High blood pressure	
29		Conception during menstruation	+			Poor	
30		+		+			
31		+			+		
32		+		+			
33	+						
34						Cardiac disease	+
35		+	+				
36		+	+				
37		+	+				
38		+			+		
39			+				
40		+	+		+		
41			+				
42			+				
43			+			Kidney disease	
44			+				+
45			+				
46			+		+		
47			+	+			
48			+	+		X-ray treatment	
49					+		+
50						Kidney trouble	+
51		+	+				
52			+				
53		+			+		
54	+						

women had previously had one or more miscarriages or that the pregnancy which terminated in the birth of a mongoloid was threatened by abortion, it will be seen that the mongoloid is born under conditions which may be recognized in advance. These mothers are known to all obstetricians as the women with habitual abortions and inability to have children

It may not be mere chance that of all additional factors which repeated themselves we find thyroid disorders (hypothyroidism) mentioned four times and ovarian cysts, or ovarian "trouble," also mentioned four times. Poor health during pregnancy was not a significant item.

CHAPTER XI

PRINCIPLES OF TREATMENT

Before we enter into a discussion of possible forms of treatment for the child with mongolism, several theoretical points must be clarified The treatment of children with mongolism has met with much opposition and has been the subject of often highly emotional controversy. It is the opinion of a number of leading physicians that such treatment is not only useless but even wrong from a theoretical point of view.

If one attempts to find reasons for this rather strange viewpoint on the part of physicians who are dedicated to helping their patients even under the most adverse conditions, one is unable to discover any sound rationale for such a pessimistic attitude. For even if mongolism were a congenital malformation or a mutation, its treatment would be justified, since treatment of many conditions of a similar nature has proved quite successful. Not only have many genetic-metabolic disorders been corrected by adequate therapy, but congenital malformations have been successfully corrected by surgery and [illegible]

evidence that what we call

fetal growth and represents

a disturbance of central growth regulation A possibly abnormal chromatin distribution in the nucleus of the cell may provide clearer understanding of the metabolic disorder seen in mongolism. If there is a redundancy of chromosomal material—the molecular representation of genes and enzyme systems—the supernumerary chromosome is certainly a disturbing factor within the cell metabolism The unusual anomalies of the nerve cells, for instance, indicate disturbances of water metabolism. Other observations indicate abnormal cellular activity. We do not yet know what enzymatic systems are possibly represented by the reported supernumerary chromatin material, but any enzymatic disorder requires further study of the abnormal molecular metabolism of the mongoloid organism. The rationale of therapy will not be worked out until the details of the pathology are definitely understood. However, even at the present time the de-

Other observations on the relationship between nutrition and the incidence of congenital anomalies indicate a definite relationship between maternal conditions and the occurrence of anomalies of the central nervous system. Among the nutritional deficiencies, we must consider not only general factors but specific factors like vitamins (vitamin A) and minerals. It is not possible at the present moment to evaluate all the factors. The steadily rising number of animal experiments, in which chromosomal anomalies are produced through various noxious agents, indicates that a great many factors must be considered as possible causative agents, and each instance of mongolism must be studied individually with great care.

SUMMARY

All the factors under consideration indicate that mongolism is not an entirely unpredictable event which comes "like a bolt out of the blue." The collected evidence (among which are advanced age and an antigenic correlation between the mother and the mongoloid child) suggests that the primary disorder may lie in oogenesis. Such disorders occur if a pregnancy is initiated under adverse health conditions.

If the mother of a mongoloid child wishes to have more children, she should undergo a thorough physical examination which includes a study of endocrine functions. Irregularities in menstruation, ovarian cysts or other symptoms may indicate a condition which is not favorable, and the mother's general health should be well established before a new pregnancy is undertaken

of stigmata occurring in those mongolians with highest test intelligence."

If the child with mongolism has a very severe congenital heart defect, his mental development is impaired through several factors. First of all, the vascular deficiency associated with a circulatory and therefore nutritional disorder of the nervous system in itself impairs mental progress Studies of the mental development of children with congenital heart defects without mongolism have provided evidence that the circulatory deficiency often causes a severe structural and functional disorder of the nervous system, resulting in impaired mentation Furthermore, a severe congenital heart defect interferes with the use of therapeutic agents and with the activities of the child A child who is often ill and restricted in his contact with other children falls further back in mental development than those chil-

ed activities

be definitely established

to the final outcome in

mental development cannot be made for several years Only then can a correct evaluation of mental potentialities be made. On the other hand, the newborns and infants with inconspicuous physical signs—those children who look *almost* normal—are very promising with regard to physical improvement. With treatment they may become rather good-looking children and adolescents whose basic condition can be recognized only by the experienced observer

All these factors must be taken into consideration in order to understand the difficulties encountered in treatment and to make proper evaluation of the results.

What can be expected from the treatment of a mongoloid child? From a physical point of view, the child will grow more adequately, will have a more normal appearance and be less prone to infection, constipation, dry skin, scrotal tongue and raucous voice. From a mental point of view, the range of treated cases lies between that of untreated cases and the norm, as diagrammatically shown in figure 85. Observations at hand indicate that the majority of untreated mongoloids have IQ's between 35 and 45 and that only a few reach a mental age of more than 5 years The results of careful treatment, carried out over several years, lie halfway between the level reached by untreated patients and that of a normal child

The treatment of the mongoloid is not merely a matter of medication. Modern child psychiatry has accumulated evidence that early institutionalization, lack of emotional mothering, premature separation from parents, rejection, and other psychodynamic factors affect

celeration of postnatal growth and the organism's lack of responsiveness to its own hormonal stimulation require supportive therapy that *accelerates growth and differentiation.*

It is, of course, unfortunate that any therapy—no matter how soon instigated after birth—is still rather late to be effective since the organism of the baby has been under the influence of a faulty metabolism for many months before birth. Some of the damage to the organism, for instance to the central nervous system, is irreparable, and much of the deceleration in development cannot be overcome in postnatal life. However, there are degrees of retardation, and it becomes more and more apparent that mongoloid children differ among each other to a much greater extent than originally supposed. Physical and mental development vary in different patients. The child with mongolism is not a "Mongolian idiot" as still so often stated in the literature, nor is he necessarily so much retarded that he is to be classified only as a trainable child. Quite a large percentage of children with mongolism have IQ ratings of over 50, and some may occasionally approach borderline intelligence. Since I do not believe in classifying children with normal intelligence and some of the stigmata of mongolism as mongoloids, it follows that the diagnosis of mongolism encompasses mental retardation to some degree. From a physical point of view, the diagnosis is based on certain physical characteristics which are always present but may be slight and inconspicuous. With proper supportive therapy of the child with mongolism, these signs may be so inconspicuous that laymen and even physicians may not recognize the condition.

In the earlier stages of research on the effectiveness of treatment, I was under the impression that the children with the least conspicuous physical features would reach the highest intelligence levels, whereas those with many congenital malformations would have poorer prospects. It must be mentioned that there is no absolute correlation between physical anomalies and mental potentialities. Some children with rather striking mongoloid features reach higher intelligence levels than others who at first seem rather little affected The anomalies of the brain and resulting mental retardation are severe in some of the most attractive children with mongolism, and the results of treatment—perhaps satisfactory as far as physical aspects are concerned—are discouraging in regard to mental progress

This is borne out by Gibson and Gibbins in their study of "The relation of Mongolian stigmata to intellectual status," which points to the paradoxic observation that "linear regression analysis demonstrates a significant relation in the direction of the greatest number

of stigmata occurring in those mongolians with highest test intelligence."

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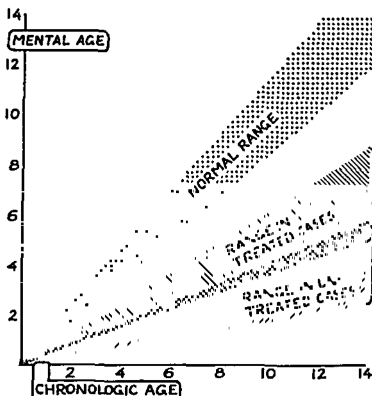


FIG. 85 —Expectation of range of mental development in untreated and treated mongoloid children compared with normal development

the development of any child in intelligence and personality structure. The mongoloid child, so much more dependent than other children, needs even more psychological support; and "treatment" should include education, emotional security and care and medication. Each factor alone is not enough, but surprising results may be obtained when all are combined It is of little use to begin treatment if early institutionalization is indicated, since large state institutions are not able to apply to all patients a treatment which is still in an experimental stage. If, on the other hand, the parents plan to keep the child at home for possibly six to eight years, better development is produced by early treatment, though the significance of the results cannot be evaluated until six to 10 years have elapsed.

THYROID TREATMENT

Unfortunately the armamentarium of our pharmaceutical industry is limited with regard to physical and mental growth stimulants Thyroid hormones are important in growth regulation but do not produce growth in themselves They influence the proliferation of car-

tilage cells and their transformation into bone. Without thyroid the cartilaginous borders remain dormant or degenerate. Thyroid stimulates the development of the vascular tree and has a strong influence on all metabolic processes, especially fat metabolism. Without thyroid hormones, the pituitary hormones are ineffective in their action upon the target organs—especially the gonads and adrenals—bone growth and general cell metabolism. Since anatomic studies as well as x-ray observations indicate that all the functions mentioned above are inadequate in the child with mongolism, thyroid therapy is indicated to activate the growth potentialities and stimulate general cell metabolism The criticism that mongoloid children become restless and aggressive through thyroid therapy is completely unwarranted [illegible] ldren are [illegible] function

[illegible] many physicians feel that thyroid treatment is justified only if available tests, such as determination of protein-bound iodide or thyroid uptake of I^{131}, indicate a true thyroid deficiency. As demonstrated before, these tests are often noncontributory or inconclusive because (in contrast to cretinism) the child with mongolism has a thyroid which produces some thyroid hormones, which are inadequate, however, from a functional point of view In the majority of cases, there is sufficient colloid formed and thyroid activity present to keep the protein-bound iodide serum level within the normal range, and yet observations suggest the presence of clinical hypothyroidism [illegible] oid- [illegible] of [illegible] Anyone familiar with mongolism must concede that of the 10 listed symptoms, the first eight are found in practically every mongoloid infant and young child. It is for this reason that mongolism, cretinism and hypothyroidism have so often been confused and not properly diagnosed. Prolonged icterus is rare in mongolism, and goiter is never found in mongoloid infants and children but occasionally in adults, while it is also quite rare in sporadic cretinism

In further discussion of specific symptoms, Lowrey and co-workers refer to the heart rate, which is often reduced in children with idiopathic hypot[illegible] [illegible] termia, fre- [illegible] heat regu-

The administration of small doses of thyroid—about 1 to 1½ grains —usually has an immediate beneficial effect in overcoming constipa-

TABLE 37 —*Symptoms in Hypothyroidism**

Symptom	49 Cretins (%†)	100 Normal Infants (%†)
Lethargy	96	0
Constipation	92	2
Feeding problems or failure to gain	83	5
Respiratory problems	76	6
Dry skin	76	1
Thick tongue	67	0
Hoarse voice or cry	67	0
Umbilical hernia	67	8
Prolonged icterus neonatorum	12	0
Goiter	8	0

* According to Lowrey and co-workers, p 132, A M A J Dis Child *96* 131, 1958.

† The percentage figures indicate a positive response obtained in the history or noted by parents during the first six months of life in the 49 cretins studied and the 100 infants chosen at random from the university hospital well-baby clinic

tion, dry skin, sluggishness and lethargy, and preventing development of the thick scrotal tongue and raucous voice. Thyroid therapy further increases the growth response of the osseous system. Dentition may appear within a few weeks after the beginning of thyroid therapy in infants who often have no teeth or only one or two up to the age of 1 to 1½ years.

X-ray studies of mongoloid infants often reveal the presence of the first two metacarpal centers at the age of 3 months, while many normal infants do not reveal these centers before 6 months of age. The significance of this observation has not yet been established Further observations indicate that the mongoloid child is often two or three years of age before any new metacarpal centers appear, and only a small radial epiphysis may develop after completion of the first year. Thus after the age of 6 months, the mongoloid child usually shows a retardation in bone age. Under thyroid therapy, the bone age becomes normal. X-ray observations are therefore very helpful in checking the efficacy of thyroid treatment at regular intervals In mongoloid children of more advanced age, x-ray observations enable the physician to check on advanced ossification, which is undesirable since it may lead to a premature cessation of growth

The beneficial influence of thyroid therapy far outweighs its untoward effects. It improves the circulation and stimulates development of the vascular system, and this in turn has a beneficial influence on brain and liver. Even if the actual anomalies of the nervous system cannot be altered, the better brain circulation produces a greater

psychological alertness and wards off degenerative changes which are otherwise observed The same is true of the liver circulation.

Thyroid therapy prevents premature degeneration of bone cartilage and improves normal ossification Because of its influence upon absorption in intestines, general metabolism, calcium and phosphorus metabolism, and the condition of the skin, the administration of thyroid is not only desirable but necessary.

Thyroid treatment in mongolism may start with 1/10 grain, three times daily, and may be increased to 1 grain by the age of 1 year. The optimal dosage varies with different patients. I have usually found a dosage not greater than 1½ grains sufficient, while I have observed that some physicians give as much as 3 to 4 grains daily. Sleeplessness, irritability and diarrhea are indications of overdosage

After the first year, mongoloid infants frequently show a tendency to obesitas Later these children usually fall into two categories: the stocky and overweight ones whose metabolism is sluggish and who benefit from thyroid, and the thin and restless ones whose requirements are more difficult to evaluate. Against expectation, some of the latter become quieter and gain weight when treated with small amounts of thyroid Therefore, treatment is not entirely contraindicated though it must be carefully supervised in these cases.

VITAMINS

Vitamin B_{12} is said to have an influence on physical growth, but whether this is a specific action or a generalized influence on appetite and metabolism is not quite clear In combination with other therapeutic agents, vitamin B_{12} improves growth and appears to be effective in the treatment of mongoloid children.

The administration of a number of other vitamins—such as A, B complex, C, E and K—has been advocated in recent years The organism of the mongoloid infant and child is said to have a poorer absorption rate of vitamins than does that of the average child This would explain the greater need for supportive therapy and might also explain why oral therapy with pituitary powders seems more effective in mongoloid children than in normal controls, in whom some of the potent agents are destroyed in the process of digestion.

THE USE OF PITUITARY HORMONES

The pituitary gland is known to be the main source of growth hormones and the key gland in the stimulation of the adrenal cortex, thyroid and gonads. Adrenocorticotropic, thyrotropic, chondrotropic and two gonadotropic fractions are established beyond doubt. The

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pathology of the target organs, presented in previous chapters, provides evidence that the tropic hormones produced in the mongoloid organism are ineffective in stimulating development of the target glands and maintenance of their full metabolism. Whether this is due to an inadequate response of the target organs or to inadequacy of the produced hormones is not known. Studies of the pituitary in mongolism indicate that the pituitary itself is stagnant and apparently unable to discharge its hormones. This would indicate that the lack of growth regulation and stimulation lies on another level, either in the central nervous system or in the general molecular metabolism.

The application of pituitary hormones in mongolism is meant to stimulate the deficient growth rate. The vicious circle of inadequate function which is seen in mongolism must be broken at some point, and the application of pituitary hormones seems to provide a lever. It may be restated that the therapy is still in an experimental stage, and other hormones, possibly from the adrenal or gonads, may prove as efficient or even more so This is in line with sporadic reports from different countries where the application of adrenal or gonadal* hormones has been said to be quite effective.

For reasons discussed in detail in the second edition of *Mongolism and Cretinism*, I recommended as long as 20 years ago the use of calf pituitary† in the therapy of mongolism. This was because comparative studies indicated a different cellular composition in child and adult pituitaries. Thus it would seem inadvisable to use pituitary hormones from adult animals in the therapy of a growth deficiency in children, since the adult glands contain mainly sex hormones and only a small amount of growth factors On the other hand, the immature gland has a more effective growth action.

* de Moragas, J Dehydroepiandrosterone in treatment of mongolism Rev espan pediat *14*.545, 1958 The author used desoxycorticosterone acetate (DOCA) in the treatment of 61 children with mongolism, giving 50 mg intramuscularly daily for several weeks The same dosage was later given thrice weekly for a long period

† I am indebted to the Armour Company of Chicago, Ill, which has manufactured pituitary capsules on my request These were originally designated as "whole calf pituitary" and were actually collected from immature animals Due to the great increase in demand and the scarcity of young animals from which to collect this powder, the calf pituitary capsules have gradually been changed to only a fraction of the original potency, since a much higher dosage is now required My earlier studies were done with the original calf pituitary extract, and for this reason cannot be compared with present day studies

Growth factors are available for injection, but oral administration is preferable—being simpler to administer, and lacking the untoward psychological effects which may evolve from years of injections. Manufacture of an effective agent for oral administration is beset with great difficulties since potency seems to be reduced or destroyed by digestion. Moreover, pituitary powder collected from adult animals that have been fattened for slaughter seems to contain very little of the growth factor.

In order to establish the effect of combined pituitary-thyroid treatment on the growth of the mongoloid child, measurements were made on outpatient clinic children over a period of 10 years. The height and weight of each child were recorded. In previous studies, institutionalized mongoloid children were measured, but outpatient material seemed preferable since these children were living in the community with their parents and nutritional conditions in general were likely better and more varied. Moreover, since the study of the effect of treatment was also made on children at home, the material is well matched. Figure 17 (page 40) tabulates (solid squares) the height of 220 untreated children with mongolism. These children are compared with 215 (white circles) treated with pituitary and thyroid and living under conditions similar to those of the first group.

A statistical analysis of figure 17 is given in table 38. For each age

TABLE 38.—*Analysis of Height Chart (fig. 17; page 40)*

Age	Treated							Untreated						
	Total No.	Normal		Borderline		Below normal		Total No.	Normal		Borderline		Below normal	
		No.	%	No.	%	No.	%		No.	%	No.	%	No.	%
Mo.														
0-12	30	18	60.0			12	40.0	7	5	71.4			2	28.6
12-24	28	17	60.7			11	39.3	11	3	27.3			8	72.7
24-36	28	12	42.9			16	57.1	9	2	22.2			7	77.8
Yr.														
3-4	29	18	62.0	5	17.2	6	20.8	14	6	42.9	1	7.1	7	50.0
4-5	12	7	58.3			5	41.7	23	7	30.4	3	13.1	13	56.5
5-6	19	8	42.0	8	42.0	3	16.0	32	12	37.5	3	9.7	17	52.8
6-7	15	7	46.7	3	20.0	5	33.3	22	5	22.7	5	22.7	12	54.6
7-8	18	11	61.1	3	16.7	4	22.2	23	7	30.4	3	13.0	13	56.6
8-9	10	5	50.0	1	10.0	4	40.0	21	6	28.6	3	14.3	12	57.1
9-10	8	5	62.5	2	25.0	1	12.5	12	1	8.3	2	16.7	9	75.0
10 & over	18	12	67.0	2	11.0	4	22.0	46	13	28.3	4	8.7	29	63.0
Totals	215	120		24		71		220	67		24		129	

level, the number of children who are within the normal range, who are borderline and who are below normal is established. "Borderline" refers to those subjects in whom there is not more than one year of retardation in height. As is obvious from table 38, the number of children with mongolism who are within the normal range and borderline increases steadily with treatment, while less and less untreated children stay within the normal range. If we take all treated children above 10 years of age, we find that 67.0 per cent are within the normal range, 11.0 per cent are borderline and 22.0 per cent are below normal. In contrast to this, 63.0 per cent of the untreated group are below normal; and a single glance at figure 17 shows how much below normal the majority of untreated children are, while the treated ones, even if they are below the normal range, are much nearer to the border.

The reported differences are significant and provide evidence that the pituitary-thyroid-vitamin B_{12} treatment has a definite influence on the growth rate. We have analyzed individual growth rates and found that the child who is within the normal range at the beginning of treatment will be able to remain there. If he is below normal, he will maintain a normal growth rate within his own grid line, which is not true of the untreated children.

Recording of weight is likely to be misleading since a weight within the normal range in a patient who is far below normal in height betokens overweight. Only if weight and height are correlated in each individual case does it become apparent that the proportion between weight and height is much more favorable in the treated than in the untreated cases.

INFLUENCE OF TREATMENT ON MENTAL DEVELOPMENT

While the influence on physical development is beyond doubt, the influence of hormonal therapy on mental development is more difficult to establish beyond criticism. The influence of hormonal therapy on the maintenance of IQ levels is indicated in figure 29. But before we can even begin to analyze the data at hand, it must be remembered that many children have IQ ratings between 30 and 50 at the beginning of treatment. To improve IQ ratings of this type would mean not only a maintenance of the mental development at a normal rate but acceleration of mentation beyond average, which seems quite difficult to achieve.

In order to determine the mental growth of the untreated mongoloid, we have conducted two separate studies. One was done with Doro-

thy Durling at the Wrentham State School, where all mongoloids of 16 years or above were examined and their mental development retrospectively charted. Of 62 patients on whom reliable data were available,

> 47 per cent had a mental age between 0 and 3 years;
> 29 per cent had a mental age between 3 and 4 years;
> 11 per cent had a mental age between 4 and 5 years;
> 9 per cent had a mental age between 5 and 6 years;
> 2 per cent had a mental age between 6 and 7 years;
> 2 per cent had a mental age between 7 and 8 years.

This means that 96 per cent of the institutionalized patients who reached 16 years or more remained on a mental level below 6 years. Details of this study revealed that the whole number could be divided into three groups.

> Group 1 reached a peak of development before a chronologic age of 16 years, usually between 10 and 15, after which no further progress was observed These patients all remained far below 5 years mentally.

> Group 2 reached a peak around the age of 18 years, *showed* progress up to that age but no further, and often showed a certain amount of deterioration. None of these patients exceeded a mental age of 5 years

> In group 3, further progress was observed after 20 years of age. These patients gained *steadily*, some up to an age beyond 30 years A certain number reached a mental age above 6 and some as high as 7 years

One possible objection which may be made to the use of this study is the fact that it was *done on institutionalized* patients, many of whom had been in an institution for over 10 years. It is well established by modern psychiatry that the institutionalized patient does not show his best development because "hospitalism" deprives him of his best opportunities Since the study of treatment was made on patients in the community, the material for comparison should also be taken from a community group. We have therefore collected data on almost 200 patients who live with their families and came to our outpatient clinic for a single examination for further advice and

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appropriate in every case and at every age level. The therapy is not a "cure" but a measure to provide optimal mental and physical development.

Two control studies have been reported: one by Eduard Blumberg and one by C. H. Carter and M. C. Maley.

Blumberg, in his study of "Two years of pituitary gland therapy in mongoloid children," observed evidence of improved growth rates and physical development. It is too soon to evaluate the effect on the mental status, since the investigation has been going on for only two years.

Carter and Maley published a "Preliminary report on treatment of mongoloids," in which they give an account of daily dosages of as much as 4 grains of pituitary to 26 mongoloid children. This is a much higher dosage than the one used in my study but seems justified because of the reduced effectiveness of the medication. The authors not only saw a satisfactory influence on the physical appearance if treatment was started in children under 4 years of age, but also observed a definite influence on the mental development. The influence on physical aspects was most marked in the young age group and negligible in the older ones. There was a definite improvement in mental development in a number of patients, and some of the final IQ ratings reported by Carter and Maley are within the normal range.

OTHER THERAPEUTIC MEASURES

Glutamic acid attracted considerable interest 10 to 20 years ago, but accumulated observations indicate that glutamic acid has no lasting influence on the mental development of children with mongolism. It goes without saying that it does not influence the physical development.

X-ray treatment had been recommended by von Wieser in 1928 but, with the exception of a study by Ira Kaplan, there have been no publications with regard to the benefit of this procedure.

NEW EUROPEAN TREATMENT METHODS

A new form of therapy has attracted considerable attention and is used for the treatment of mongolism in some European countries, especially in Germany, and also in South America. The injection of embryonic cells from freshly killed animals was originally devised for many different conditions. The cellular therapy is now available in a dried form known as "Siccacell."* H. Haubold, who calls this a "post-

* Manufactured by Pharmakon, Ltd., Zurich, Switzerland

planning. This material seems ideal in respect to the question of how well the mongoloid child develops in the community under optimal conditions without treatment. The results are presented in figure 29, together with the mental progress of 50 treated mongoloids.

Many aspects of this chart are worth discussing. The study of the untreated mongoloids shows again that at the age of 1 year, none had reached a mental level higher than 6 months. Even at the age of 2 years, none had passed the 1 year psychologic mark. The surviving mongoloid child progresses at a rate of 30 to 50 per cent after 2 years, and at 4 years of age some have reached a mental level of 2 years or even a little more. On an average the IQ level of the untreated mongoloid is within 40 to 55 per cent, with a few patients doing a little *better and a number of patients failing completely in their development.* In this study, only one of the 200 ambulatory cases had a Stanford-Binet mental age above 5 years, and this child had had some treatment early in life but no systematic follow-up.

The treated group consists of children who were being kept in the family as long as possible and for whom everything possible was being done. Children with severe congenital malformations were excluded from treatment. Treatment, consisting of daily dosages of 1/10 grain thyroid and 1 pituitary capsule, was started as soon after birth as possible. By the end of the first year, the dosage had been increased to 1 to 1½ grains thyroid and 2 pituitary capsules. Specific instructions were given that the pituitary was not to be administered in single doses.

In studying figure 29, it will be seen that the treated children continue to make progress after an age of 6 years, whereas the mental age of the untreated patient levels off and remains below a mental age of 5 years. From a statistical point of view, the effects of treatment do not appear significant until several years of treatment have elapsed and a chronologic age of over 6 years has been attained. However, parents and physicians often notice the effect of treatment within a few weeks of its inception. The infant becomes more active and alert, his expression is more vivid, and he seems to respond more readily to stimuli.

Since it is mainly intended to overcome the stunted growth and improve physical appearance and mental performance, the treatment should be instigated as early as possible in infancy and carried out over the first eight to 10 years. The older the child, the fewer the changes that can be expected. The treatment must be individualized according to the needs of the patient, and no standard therapy can be

appropriate in every case and at every age level. The therapy is not a "cure" but a measure to provide optimal mental and physical development.

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* Manufactured by Pharmakon, Ltd , Zurich, Switzerland.

maturation therapy" ("Nachreifebehandlung"), has developed a specific technic. The child is first built up by the application of a variety of vitamins, and chronic and intercurrent infections are completely eliminated. The child then receives a series of four or five injections of Siccacell intramuscularly on four or five subsequent days. Treatment is continued through the application of multivitamins, and a new series of injections may be given after six to 12 months.

Siccacells and similar agents are called "Regenereses," but the term Regenereses* is apparently also used as a trade name.

According to Dyckerhoff, regenereses are

Cellular extracts containing those enzymes which act as catalysts in the synthesis of proteins After removal of the accompanying cellular substances, regenereses are prepared in sterile aqueous solution and contain no more than traces of proteins. Most of the protein is eliminated by special processes, in the course of which, however, the active cellular biocatalysts are retained by the most sparing of chemical treatments. Regenereses therefore differ basically from so-called hydrolyzates and other cellular tissue extracts in which, together with the destruction of the protein by acid or alkali hydrolysis, a large proportion of the coenzymes and other active principles are also destroyed For this reason alone, any comparison between regenereses and the many hydrolyzate preparations available commercially is misleading.

Haubold's reports of Siccacell injections in over 100 cases of mongolism are very optimistic, but it is not yet possible to evaluate the effectiveness of the treatment and decide whether it is superior to others. It must be remembered that most of the children given Siccacell therapy had not been treated before and are often quite dys plastic. Rather spectacular results will therefore be produced in the beginning if any attention is given to the child and any therapeutic procedure is adjusted to his needs This is also true of other therapeutic measures which are recommended by different physicians who give no details of their procedures.

In summary, it may be said that the pharmacologic treatment of mongoloid infants and children is still in an experimental stage, and no therapeutic method can be considered a definite solution. It must be stressed, however, that the therapeutic goal is well defined and consists of the need to accelerate physical and mental development and to activate the delayed maturation It is hoped that extensive research on the pharmacologic needs of the mongoloid child will result in the development of a therapy which will produce more satisfactory maturation and growth of these children.

* Manufactured by Chemische Pharmazeutische Fabrik, Koln-Braunsfeld

EDUCATIONAL AND PSYCHIATRIC ASPECTS

From the collected observations, it is evident that the child with mongolism needs more than drug therapy. Although therapy has a considerable role in the program of habilitation, proper education and psychiatric handling of the child and the family situation are also important The psychological needs have been pointed out in chapter V, and some suggestions have been made There is also a discussion of education, and whether these children should be brought up in institutions or in the community. A few pertinent points may be restated and summarized.

Hormonal and chemical therapy alone are not sufficient to produce the optimal mental development of the mongoloid child. Special attention must be given to his emotional needs and to his peculiarities in learning It must be remembered that these children are subject to the same emotional factors which psychodynamic psychiatry deems essential in the upbringing of normal children Their needs for affection, love and consideration are great. Those who are loved are usually trusting, quiet and loving, and have no difficulty in establishing contact with their surroundings and securing interest and affection from others.

If a mongoloid child finds himself unacceptable, this awareness will have an unfortunate influence on his development. Some of these children are restless and destructive, running from one place to another and tearing everything apart, the despair of everyone who comes into [illegible] d that the [illegible] informed [illegible] Mongolian idiot" will never amount to anything and should be "put" *into* an institution immediately after birth. The parents feel guilty and wish to conceal the fact that the child is not normal. They are constantly correcting the child, but fight a losing battle, and the influence of their attitude can often be seen in the behavior of the patient as well as in the attitudes of the siblings If the parents quarrel over the defective patient and regard his presence in the family as disturbing and shameful, the older children quickly adopt such an attitude as their own Then, too, neighborhood children and friends are often disrupting influences, and many difficulties arise from the unfriendly attitudes of others. On the other hand, the older siblings are usually quite willing to accept the situation [illegible] bestow their affec[illegible]

[illegible] disease and needs special attention

During the preschool years, the mongoloid child develops more slowly and needs more time than the average for each step. He must be considered a preschool child up to about 8 years of age; and realizing that the average developmental quotient is about 50 per cent or less, the parents will know what to expect and that the child must be looked upon as much younger than his chronologic age. The well-cared-for mongoloid learns to walk between 2 and 2½ years and sometimes sooner, and to talk between 2½ and 3½ years. Although he cannot be expected to enter school at 6 years of age, some of these children are on kindergarten level at that age and may be on a first-grade level at 8 years or soon after.

The mongoloid's scholastic capacities are less well developed than his potentialities for social maturation. Many of these children have a good memory and can acquire a large vocabulary and learn to spell well Because arithmetic and the concept of quantities are the least developed and offer the greatest difficulties, such children will be most handicapped in the handling of money Education as a whole should utilize everyday material and be concentrated on the development of concrete conceptions. Abstract thinking will always be limited All these facts must be taken into consideration in the teaching of language and reading. The main goal should be development of practical skills, and reading and arithmetic should not be stressed. A mongoloid adolescent with a pleasing personality can be quite helpful around the house, especially in rural environments, and may be able to remain in the community Should it be evident that the youngster will not be able to remain in the community and must eventually be admitted to an institution, it is better to take such a step when the child is in his 'teens than to wait until he is 20 years of age or older, when he may find it very difficult to adjust Moreover, the psychological and emotional isolation of some of these persons is such that it would be preferable for them to join an institutional group in which they will find others of the same mentality as well as a wealth of occupational facilities and entertainment

There is no justification for the attitude that all efforts are useless if a child is not perfectly normal Great successes have recently been achieved in the field of cerebral palsy Can we not hope for similar successes in the field of mongolism? More consideration should be given to the problems of the mongoloid child Many children with mongolism are educable, others are trainable The mongoloid learns by imitation and from the example of others, and it is amazing to see how much he can develop when proper attention is given to his needs

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